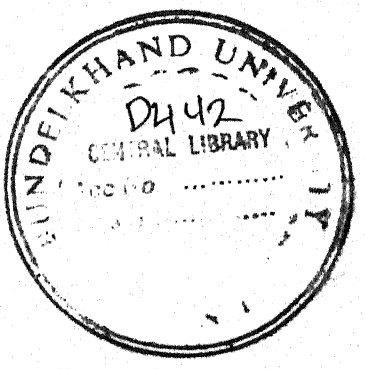
A CLINICAL STUDY OF EPIDURAL MORPHINE, PETHIDINE, PENTAZOCINE AND FENTANYL FOR POST—OPERATIVE ANALGESIA

THESIS
FOR DOCTOR OF MEDICINE
(ANAESTHESIOLOGY)

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1983





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CERTIFICATE

This is to certify that the work entitled " A CLINICAL STUDY OF EPIDURAL MORPHINE, PETHIDINE, PENTAZOCINE AND FENTANYL FOR POST OPERATIVE ANALGESIA " has been carried out independently by Dr. Usha Rani Sharma in this department.

She has put in the necessary stay in the department according to the University regulations.

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INTRODUCTION

INTRODUCTION

" For all the happiness,
Mankind can gain,
Is not in pleasure -
But in rest from pain. "

Pain has been the most distressing symptom which has attracted the attention of the humanity since its evolution. The pain relief has been a constant problem which is a matter of great research in medical profession.

Treatment of pain offers many worthwhile oppertunities for anaesthetists for active participation in helping those, in distress.

There are various theories of pain mechanism, but none is explanatory. According to Sherrington, (1906) - 'Pain is the psychical adjunct to an imperative protective reflex.' Pain is a specific mode of sensibility, distinct from other sensory modalities such as tough, warmth and cold. Pain can not be defined in words which would mean anything to a person, who has not experienced it. It is a subjective affair, though it may be accompanied by measurable physiological responses such as reflex

withdrawl of movements, changes in vasomotor tone, blood pressure, heart rate, breathing and sweating etc.

The management varies according to the difference in the quality of pain. Correctly diagnosed acute cases may be cured with prompt treatment. The conventional methods, be it by drugs, injections, surgery or other means, have their own limitations.

The analgesics like opiates etc. have their own hazards of limited potency, tolerance, addiction, side effects and need for repeated dosage. Moreover the conventional analgesics are tried only after the onset of pain, where they become less effective on account of the increased pain threshold. This handicap leads to an increase in dosage, augmenting the occurence of complications like respiratory depression. This shortcoming is further enhanced by the need of repeated pricks, disturbing the patient and involving close nursing care, normally not always at hand.

The identification, by Synder, of specific receptors which are sensitive to

narcotics, in the substantia gelatinosa of posterior horn cells of spinal cord, in 1975, has opened a new concept of treatment of pain by introducing the pain-killers intrathecally or epidurally. The major drawback of intrathecal route is the direct introduction of infection to nervous system. Epidural analgesia, therefore, comes far ahead and marks the beginning of a new era. Epidural analgesia blocks motor, sensory and autonomic systems, with the added advantage that its effect vanishes after some time (Crawford, 1975; Taylor, 1977 and Thornburn, 1980).

Not only local anaesthetic agents can be administered epidurally, but also analgesic agents like morphine (Behar, 1979; Bapat, 1979; Jean, 1979; Johnston, 1979), pethidine (Cousins, 1979), fentanyl (Wolfe, 1979) and dilaudid (Leslie, 1979).

Epidural injections of these agents are required in much smaller doses as compared to the quantity required for other conventional routes, resulting in the minimisation of various side effects. It is further selective in blocking the pain pathway only, with no adverse effect on

pulse, blood-pressure and muscle tone. Alleviation of pain further increases the vital capacity. The cough-reflex is not hampered, thereby reducing the occurence of post-operative pulmonary complications. Epidural analgesia has an extra advantage of being useful in cases where pain is not responding to analgesics administered through conventional routes.

The present study has been undertaken to mark the supremacy of epidural analgesia over conventional methods, mainly in the post-operative cases.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

'Pain is perfect misery, the worst of all evils and excessive overturns all patience.'

(John Milton: Paradise Lost)

Historical review:

The same was realized by the primitive men also, who used massage and herbs to relieve it. The use of analgesics goes back to 2250 B.C., in the maiden record of the Babylonian clay tablet from Nippur. The analgesic pills were first referred by Celsus in his De Medicine (first century A.D.). The importance of the central nervous system for pain was realized by Galen (second century A.D.), who performed experimental cordotomy. William Harvey, overwhelmed by his circulation discovery, announced heart to be the sole culprit for pain. A step forward was the concept of " delicate threads " for the transmission of sensation, reproduced by Discartes in 1644. Contrary to all beliefs, Chinese consider the evil of pain as recent guest, easy to expell out by acupuncture through 365 suitable points.

With the dawn of nineteenth century, the actual strategy of pain control grew up from its

childhood. Charles Bell (1811) laid his emphasis on dorsal roots of the spinal nerves, being distinct from ventral roots in function. Johannes Muller expounded the theory of specific nerve energies which was later disproved.

By the sunset of nineteenth century, pain perception was explained by three different ways in the form of emotional experience, intensive theory and specific sensory theory. Schiff (1848) ruled out the importance of touch and found pain a distinct entity. Hlix (1884) separated pain and pressure spots over skin. Vonfrey (1894) histologically identified end organs for each sensation. Thus the concept of pain as a sensation got speed, further emphasized by Strong in 1895.

The hallmark of pain control was the first demonstration of surgical anaesthesia at the Massachesusetts General Hospital in October 1846 by William T.G. Morton. The isolation of morphine by Serturner in 1806, marked the onset of systemic analgesia. Bennett (1873) and Anrep (1878) demonstrated analgesic properties of cocaine to advance regional anaesthesia. Abbe performed posterior rhizotomy to introduce neuro-surgical technique for halt of pain.

PATHWAYS OF PAIN

Pain is one of man's most compelling experiences. It is an unpleasent sensation, which only the individual can appraise and as such is incapable of a satisfactory objective definition. (Merskey and Spear, 1967). Sherrington (1906), has described pain as " the psychical adjunct to an imperative protective reflex." This concept certainly draws attention to the protective aspect of pain.

Although the nature of pain was recognised by the great Greek philosophers, the theory that the pain can be produced by intensive stimulation of any sensory organ, has been frequently discussed. The neuro-anatomical basis of pain sensibility has been unfolded in the past, following the discovery of sensory functions of the posterior spinal nerve roots and the existence of medullary pathways comparatively specialized for pain.

The receptor organs for pain are distributed throughout the body, but it is convenient from the clinical aspect to consider pain under the following headings.

A. Superficial or cutaneous pain.

B. Deep pain (Muscles, Bones, Ligaments, Joints and fascia).

C. Visceral pain.

D. Referred pain.

E. Psychogenic or functional pain.

The physiological mechanism and the neural pathway for reception, conduction and appreciation of painful stimuli, irrespective of the site of its origin, are same, and therefore the description that follows is common to all types of pain.

The neurophysiological mechanism can best be understood under the following headings.

(1) Reception of pain:- The superficial, deep and visceral tissues are studded with the network of non-myelinated or poorly myelinated nerve fibres, responsible for the transmission of pain. These fibres respond to a variety of excessive stimuli e.g. thermal, mechanical, electrical or chemical.

The exact nature of the response whether by direct excitation of bare nerve endings or by tissue damage with secondary release of pain producing substances, is not clearly understood. Although Hardy and others (1951), by working with thermal energy, concluded, that the onset of pain coincided with the temperature at which alterations in tissue protein

started taking place. As a result they anticipated release of pain producing substance. But, Beecher (1956) rejected this theory and pointed out that extensive tissue damage can be produced without pain being experienced. He blaims the level of anxiety as being responsible for the occurence of pain. Wolf and Wolf (1958) consider that in such extensive injuries, coagulated serum, oedema and devitalized tissue may shield the pain endings from noxious stimuli. Moreover, damage to nerve terminals and fibres may desensitize traumatised tissue.

A pain producing substance, probably a polypeptide, has been detected by Armstrong and his co-workers (1957) in inflammatory exudates. They have also held several other substances, like histamine, acetylcholine, angiotenin, bradykinin, adenosine triphosphate, serotonin, hydrogen and potassium ions and 5-hydroxytryptamine, responsible for producing pain (Armstrong et al., 1953). Recent evidence (Ferreira, 1972), suggests that prostaglandin E, sensitizes the pain receptor to stimuli such as pressure and also the action of chemical mediators.

(ii) Conduction of pain:- Pain is conducted from the receptor site to the spinal cord, and thenceforth,

through various ascending pathways to the sensory cortex for its perception, by means of mixed nerves which act as transmitting cables.

These mixed nerves are collection of various types of fibres both myelinated and non-myelinated, and Gasser (1943), has classified these fibres into three broad groups depending upon the diameter and the conduction velocity of nerve impulses. The classification is as follows:-

Terminology	Fibre	Diameter (in μm)	Conduction speed (in meters/sec.)
Myelinated somatic fibres A	Alpha	20 μm	120
	Beta		
	Gamma		
	Delta	3-4	16-30→pain fibres
	Epsilon	2 μm	5
Myelinated visceral fibres B (Pre-ganglionic autonomic)		< 3 μm	3-15
Non-myelinated somatic fibres C		< 2 μm	.52→pain fibres

Two groups of fibres are responsible for the transmission of pain. These are -

(a) the myelinated A delta fibres which have the diameter of 3-4 um and conduct at the speed of about 35 meters per second.

(b) the more slowly conducting C fibres which are unmyelinated, have a diameter of less than 2 um, with a conduction velocity of .5-2 meters per second.

The existence of both fast and slow neural pathway for conducting pain impulse to the central nervous system, is suggested by the occurence of a double pain sensation, so called the 'echo pain'. The term applies to the twin peaks of pain which may follow the brief pain stimulus to the skin. Landau and Bishop (1953), concluded from their experimental study that C fibres-pain had a delayed, burning and persistent character, while the one transmitted through delta fibres is sharp and pricking in nature.

(iii) Central nervous system :-

(a) Transmission in spinal cord:- All the primary sensory afferents have their cell bodies in the dorsal root ganglion of the spinal cord. Pain fibres enter the spinal cord via the dorsal root, and then ascend or descend for one or two segments in the medial portion of Lissauer's tract to enter the more ventrally placed dorsal horn. Medial portion of Lissauer's tract carries excitatory fibres from adjacent roots, while lateral

portion carries inhibitory fibres.

The second synapse is formed in the substantia gelatinosa at the tip of dorsal horn, after the fibfes have traversed 1-3 segments. The axons of the second neuron cross the mid line in the anterior commissure to form the lateral spinothalamic tract, which ascends and terminates in the lateral nucleus of the thalamus.

The spinothalamic tract is characteristically divided into two-

(a) The neospinothalamic tract-which arises from the dorsal horn, occupies the antero-lateral quadrant of the spinal cord. The axons terminate in the ventrobasal complex of the thalamus. This tract perceives the intensity of pain and localises it.

(b) The paleospinothalamic tract-which originates from the dorsal horn, receives c fibres input, crosses the anterior commissure and ascends in the spinal cord closely applied to, but more ventral than the neospinothalamic tract.

The fibres, after giving collaterals to the reticular formation of the brain-stem, terminate in the central, lateral and the intra-laminar nuclei of the thalamus. This pathway transmits the arousal and emotional component of pain.

A third spinal ascending pathway which may play some role in the nociception, is the spino-reticular pathway which consists of projections from small myelinated and unmyelinated fibres in the dorsal horn, mostly ipsilaterally and to a lesser extent contralaterally. The fibres terminate in the brain stem reticular formation, particularly in pons and medulla.

The grey matter in the spinal cord is arranged in the form of 10 laminae. Lamina 10 is arround the central canal, lamina 9 is the motor neurons while 7 and 8 are the interneurons. The dorsal horn, as it is classically known as, is laminae 1-6. Laminae 1,2 and 3 form the substantia gelatinosa; 4,5 and 6 form the nucleus proprius with clarke's column in 6. Laminae 1-6 receive the primary afferent neurons and the cells in each layer converge on the layers below. Each lamina is activated by its own afferent neurons and a particular level of activity is achieved in this fashion (Sampson Lipton, 1976).

(b) <u>Reticular system</u> - The fibres originating in the brain stem reticular formation, receive input from several sources, including almost certainly, the paleospinothalamic and spino-reticular pathways;

ascend in polysynaptic projections to the wide area of thalamus. This provides an alternative route for pain impulses to bombard a large area of the cerebral cortex. It is believed that stimuli following this pathway activate the cortex and help to maintain consciousness; this is probably a non-specific arousal mechanism.

(iv) Thalamus and the sensory cortex - Consciousness of pain is experienced at the level of thalamus, which contains a series of nuclei; a number of these are known to be involved in the appreciation of pain. Ascending reticular fibres form two groups, one of which is distributed to the intralaminar nuclei of thalamus while the other passing to the hypothalamus. Spinothalamic tracts terminate in the posterolateral ventral nuclei of thalamus before relaying onwards and the posterior column fibres also terminate in the thalamus. Thus it can be appreciated that all sensory fibres converge on the thalamus.

After relay in the thalamus the sensory fibres project onto the post-central gyrus in the cerebral cortex, maintaining the dermatomal arrangement of the fibres. It is possible to map out a distorted image of the body in the cortex itself.

The relative importence of thalamus and cortex, in the perception of pain, is still disputed. Head (1920) believed that pain is experienced when nerve impulses arrive in appropriate part of thalamus and regarded it as the centre of consciousness for pain. Thalamic sensation is crude and poorly localised, while cortex is essential for localising and detecting variations in the intensity of pain. To ascribe sensation to the thalamus and perception to the cortex, is to take too narrow a view of a complex functional inter-relationship. The conscious appreciation of pain appears to depend upon the widespread activity of intact cortex. It thus enables the individual to interpret and formulate his own personal reaction to a particular painful experience.

The intensity of pain, suffered, varies enormously with the personality, intelligence and culture of the individual. Emotional stress and anxiety adversely effect the pain response as also debility and fatigue.

(v) Descending pathways - Descending pathways comprise of fibres which originate in the orbital frontal cortex and probably descend via cortico-spinal tracts. The fibres which originate in the mid brain reticular

formation and raphe nucleus of the medulla and descend via polysynaptic pathways, reach the dorsal horn to modulate input to all laminae of dorsal horn particularly lamina 5. These descending fibres may influence activity at the dorsal horn level via either pre or post synaptic contacts and may be either facilitatory or inhibitory.

Theories of pain -

For pain transmission, perception and appreciation, three theories were put forward.

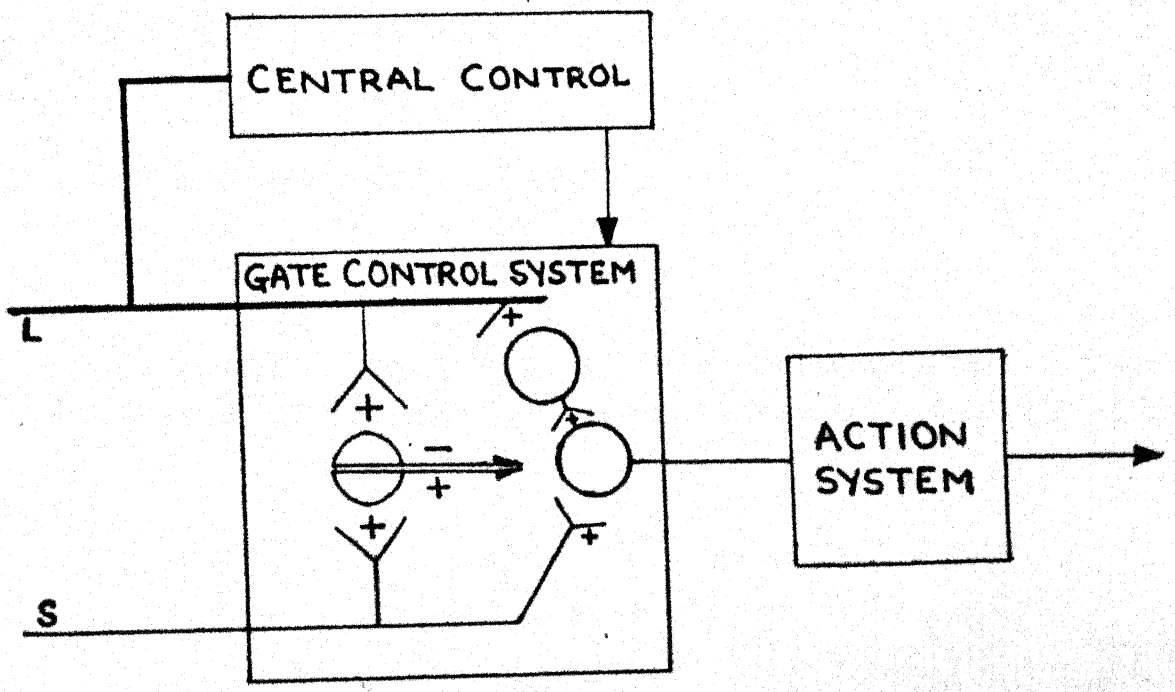
First was the 'specific pain theory' in which it was postulated that there were specific pain receptors in the skin and specialized nerves and pathways transmitted painful stimulation from periphery to spinal cord and from spinal cord to brain. It was believed that pain was perceived on a one-for-one basis.

Second was the 'pattern theory' in which it was postulated that pain sensation was coded in same fashion at the periphery as in brain and that it was the patterns of frequency and strength of the electrical stimulation passing through nerve fibres and nerve cells which ultimately were interpreted as pain.

Most recent and still accepted is the third ' Gate-control theory ' proposed by Melzack and Wall (1965), expanded in the form of a model by Casey and Melzack (1967) schemetically represented in the diagram.

In this theory, it is suggested that the sensory input from the skin is modulated by a gate control system before its eventual perception as pain. The sensory impulses from the skin are distributed to three systems in the spinal cord, the tracts of the dorsal columns for onwards transmission to the brain, the cells of the substantia gelatinosa and the first central transmission (T) cells in the dorsal horn which transmit sensory information to high centres.

The substantia gelationsa acts as a gate control mechanism. As it has been shown (Wall 1962; Mendell and Wall, 1964) that although the large fibres are at first very potent in activating the T cells, their effect is later diminished by an inhibitory process. Small fibres have excitatory effect. Continuous nerve impulses transmitting primarily by small fibres, keep the gate comparatively open. Skin stimulation evokes the volley of impulses in which large fibres activity predominates. The T cells are activated, but due to a inhibitory process



GATE CONTROL THEORY OF PAIN

L – Large diameter fibre

S – Small diameter fibre

T – First Central transmission cells

the gate is partly closed. Sustained stimulation activates small fibre system, while adaptation occurs in large fibres. Thus the gate is opened and the outflow of impulses from T cells is increased.

Central efferent fibres influence the gate control mechanism through emotion or previous experience in the form of ' central control trigger ' mediated by dorsal column (Hagbarth and Kerr, 1954; Wall, 1967).

Management of pain :-

The management of pain is still a partially solved problem. The planning of treatment depends upon the cause of pain, nature of the cause, age and psychosomatic behaviour of the patient. Various techniques are practised, each one having its own limitations.

1. Drug therapy - parenteral analgesics require repeated dosage, needing multiple pricks. The selection can be made from Diconal, Levorphenol, Methadone, Bezitramide, Phenazocine and Pentazocine.

2. Nerve blocks - are ineffective in generalized pain. They can be either chemical or electrical.

3. Electrical stimulation- procedure is difficult, giving only temporary relief. External electrical stimulation and dorsal column stimulation are two

important ways.

4. Acupuncture - a new introduction requires much knowledge and skill, less effective for chronic pain.

5. Radiotherapy - has selected implication, requiring costly technology.

6. Hypothermia, hyperthermia and psychotherapeutics- have limited scope.

7. Destructive methods - like percutaneous cervical cordotomy, rhizotomy, transnasal pituitary injections and other neurosurgical techniques are drastic and difficult.

8. Amputation- is no treatment.

9. Intrathecal methods - intrathecal phenol, chlorocresol, alcohol and cold saline or barbotage has disadvantage of introducing infection directly to central nervous system.

10. Epidural analgesia-which practically has no disadvantage and therefore is emerging like a boon to mankind.

Epidural Space -

The epidural space is the space between the periosteum lining the vertebral canal and the duramater surrounding the canal. Its cephalad extension is till foramen magnum where dura attaches

to entire circumference of foramen, caudally it continues with the sacral canal, anteriorly lies the posterior longitudinal ligament, while posteriorly are laminae and ligamenta flava, lateral limits are marked by the pedicles and forty eight inter-vertebral foramina. What makes the epidural injection safe for the therapeutic and diagnostic administration of drugs, is the anatomy of the space (Pages, 1921; Deglietti, 1933; Odom, 1940; Cousins, 1943).

The epidural space is not uniform in size and shape through out. It is triangular and widest in the lumber region (4-6 mm),(Bromage, 1954; Cheng, 1963; Macintosh, 1957). Attempts to pin point the capacity of extradural space were pioneered by Sicard and Forestier (1921). Lipiodol was injected and the volume was co-related with roentgenographic appearance. Total capacity of 118 ml for extradural space was calculated by Farr (1926) by injecting sodium iodide in fresh Cadavers.

The contents of epidural space are fat and loose areolar tissue, through which run the internal vertebral plexus, lymphatics and the dural projections, which surround the spinal nerve roots (Bromage, 1954; Cheng, 1963). In third trimester of

pregnancy and in cases of large intra-abdominal tumours, the vertebral venous plexus is engorged reducing the size of space vis a vis the dose (Bromage, 1963-64). The epidural space is a potential space with a negative pressure (Bromage, 1954; Cheng, 1963; Dogliotti, 1933; Heldt, 1928; Janzen, 1926). Only 80% of the patients have this negative pressure (Dawkins, 1971).

Identification of the epidural space -

The following points suggest that the needle is in the extradural space.

1. Sudden lack of resistance to advancing needle as it pierces the dense ligamentum flavum.

2. Sudden ease of injection of a little air or liquid from a freely running syringe attached to a needle. If the point is in ligamentum flavum, plunger rebounds, if it is in the space, plunger can be pushed in easily (Sicard and Forestier, 1922; Dogliotti, 1931).

3. Movement of the bubble on Odom's indicator (Odom, 1936), which can be attached to hub of spinal needle.

4. Brooks' modification of Odom's indicator (Brooks, 1957).

5. Withdrawl of hanging drop of saline on hub of needle (Gutierrez's sign).(Gutierrez,1932).

6. Macintosh spring loaded needle, (Macintosh, 1950), devised by R.H.Salt (Salt, 1963).

7. The Ikle syringe (Ikle, 1950).

8. The drip indicator (Dawkins, 1961).

9. Ultrasonic localisation of lumbar epidural space (Cork et al., 1979).

Occasionally small amount of clear fluid may continue to drip slowly from the needle hub, and usual physical tests such as temperature estimation, attempts at aspiration and observation of flow rate still leave doubt in the mind. The chemical properties of spinal fluid, saline solution and local anaesthetic drugs in various concentrations were compared utilizing a urine test strip (Reisner, 1976).

Solution	pH	Glucose		Protein
C.S.F.	7	0	1+	Trace- 1+
Saline soln. 0.9%	5	0	0	0
Bupivacaine .25%	5	0	0	2+
.5%	5	0	0	3+
.75%	5	0	0	4+
Lidocaine 1%	5	0	0	2+
1.5%	5	0	0	2+
2%	5	0	0	2+
Mepivacaine 1%	5	0	0	2+

Tuohy (1945) discovered his special needle which he claimed could direct a catheter in the desired direction. Henkin et al. (1970) have described a disposable epidural-anaesthesia-system which incorporates an external teflon catheter with a precurved tip. The needle tip can be hidden inside the soft catheter tip giving a blunt tipped combination which greatly reduces the chance of accidental dural puncture. Since the catheter is of larger bore than the needle, it allows for reliable aspiration of cerebro spinal fluid and blood and offers no resistance to drug injection. Use of various type of epidural catheters and their methods of sterilization have been described by Davidson et al. (1951). Teflon and Vinyl tubing may be autoclaved, while polythene tubing should be sterlized with tincture of zephiran.

Technical hazards -

1. Accidental puncture of dura - This may occur with the epidural needle or the polythene catheter (Mehre 1960, and Sanchez, 1967). Massey-Hawkins (1969) reports an incidence of 0.6% of perforation of dura by polythene catheter even though the needle had been correctly placed in the epidural space. Mehre and Saying (1960) advise that massive subarochnoid block can be avoided by injecting 2 ml. of analgesic

solution through the catheter as test dose. Epidural block should be performed under strict aseptic conditions, because of the possibility of dural puncture (Bromage, 1954).

Incidence of spinal tap is lower when visual methods are used rather than when the loss of resistance test is employed for identification of epidural space (Massey-Dawkins, 1969).

Author and year		Incidence of spinal tap
1. Chaplin and Ramwick	(1958)	1.1%
2. Lund and Quinn	(1961)	2.0%
3. Carr and Metre	(1962)	2.3%
4. Moir and Willocks	(1968)	2.3%

2. <u>Errors in cannula placement</u> -

Sanchez et al. (1967) found that an epidural catheter passed through Tuohy needle could move in the desired direction only in 47% of cases. It passed out into para vertebral space in 6.6% cases. Muneyuki et al. (1970) found that a catheter in epidural space tends to curl upon itself after 4-5 cm. Mehre and Seying (1960) reported a case, where a catheter introduced into epidural space tied itself into a true knot after more than 4 cm. of it had been introduced.

Massey- Dawkins, (1969) advises that more than 5 cm. of catheter should not be introduced.

Catheter tip was cut off in 3 cases, inside the epidural space in attempting to pull it out through Tuohy needle (Bonica et al.,1957).

3. Haematoma - It may be caused by the introduction of any needle whether or not an analgesic drug has been injected. The resulting pressure effect of haematoma within the vertebral canal, particularly in the extradural space, may compress the cord causing paraplegia.

Historical review of epidural block -

Approach to the epidural space through sacral hiatus was introduced by Corning and then used in dogs by French investigators Sicard and Cathelin in 1901. In 1920 Zweifel analysed the incidence of fatalities in caudal epidural blocks. The space was studied by Sicard and Forestier (1921) by injecting coloured solution. Practical lumber epidural anaesthesia owes its birth to Pages (1921). Later Dogliotti (1931-33), Hess (1934), Odom (1936), Gutierrez, (1939) and Harger et al. (1941), popularised the epidural technique. Heile (1913) tried to reach the epidural space by the inter-vertebral foramina.

Sicard and Castan (1904) have shown that the epidural space did not communicate with the subarachnoid space, by injecting india ink suspension into the epidural space of dogs. Same was emphasized by Sanford and Doub (1941). Bertochi (1932) found dura almost impermeable to local anaesthetics. On the contrary now it is clear that the local anaesthetics cross the dura and enter the subarachnoid space (Frumin et al., 1953 and Usubiaga, 1961-64).

Sensitive radio assay technique using C^{14} labelled lignocaine or mepivacaine showed that the concentration of local anaesthetic in subarachnoid space was nearly as high in case of intradural route as with extradural route (Bromage et al., 1963; Bromage and Burfoot, 1964). Usubiaga(1961-64) reported recovery of 7.3% of epidural procaine in the subarachnoid space. The concentration of epidural procaine was directly proportional to the recovery amount in cerebro-spinal fluid. In many cases procaine level exceeded the amount necessary to block the myelinated fibres in spinal nerve roots (Frumin et al., 1953). Thus 3-10 percent of epidurally injected substance may enter the subarachnoid space.

Moore et al., (1958) studied the spread of contrast media in the epidural space of 19 human

cadavers, 1-3 hrs.after death by injecting solutions through L_{2-3} space. With 40 ml. he could trace it from the C_7 to S_2 vertebrae. The solutions tracked out of each intervertebral foramina through the entire length of the visible shadows, irrespective of age. Nishimura et al., (1959) reported a tendency of cephalad spread of the solutions in 56.7% of cases, irrespective of the position of the patient and the direction of the needle. The contrast medium when injected through second lumbar interspace, was rarely seen beyond first sacral vertebra. Similar findings were reported by Usubiaga et al., (1964).

Yates (1965) reported visualisation of epidural space upto second lumbar vertebra without any tilt of the table by injecting 20 ml. of contrast medium through caudal route. Dutta et al., (1972) studied injected radio-opaque solutions at the third lumbar interspace before administering epidural anaesthesia and reported a tendency for cephalad spread in 66.7% of cases, with the absence of leakage through intervertebral foramina in 42.4%. They could visualise the epidural space from T_2-T_5 vertebrae with 20 ml. of injection. They further concluded that the dispersion was cephalad, even when tip of the needle was directed caudally.

The longitudinal spread of the epidural solution is dependent on the volume injected. Sharrock (1978) pointed out that the height effected the extent of epidural anaesthesia in the elderly but had no influence in the younger individuals, because in elderly patient the intervertebral foramina are not patent as is shown by radiographs taken after the injection of radio-opaque dye into the paraveretebral space. No method exists for the pre-determination of the size of intervertebral foramina and consequently the amount of solution which will leak along side of the nerves.

Bonica (1957) pointed out that the site of epidural injection should be nearest to the mid-point of the segments to be blocked, dosage being 1 - 1.5 ml. of solution per segment with a total of 12-15 ml. of solution. Caudal epidural requires 20 ml. of solution.

Fate of drug in epidural space -

The fate of an epidural injection meets primarily diffusion through dura and leakage through intervertebral foramina (mainly in young individuals). Vascular and lymphatic absorption, diffusion through villi and perivascular spaces and uptake in extra-dural fat mark the other ways of spread (Bromage, 1963).

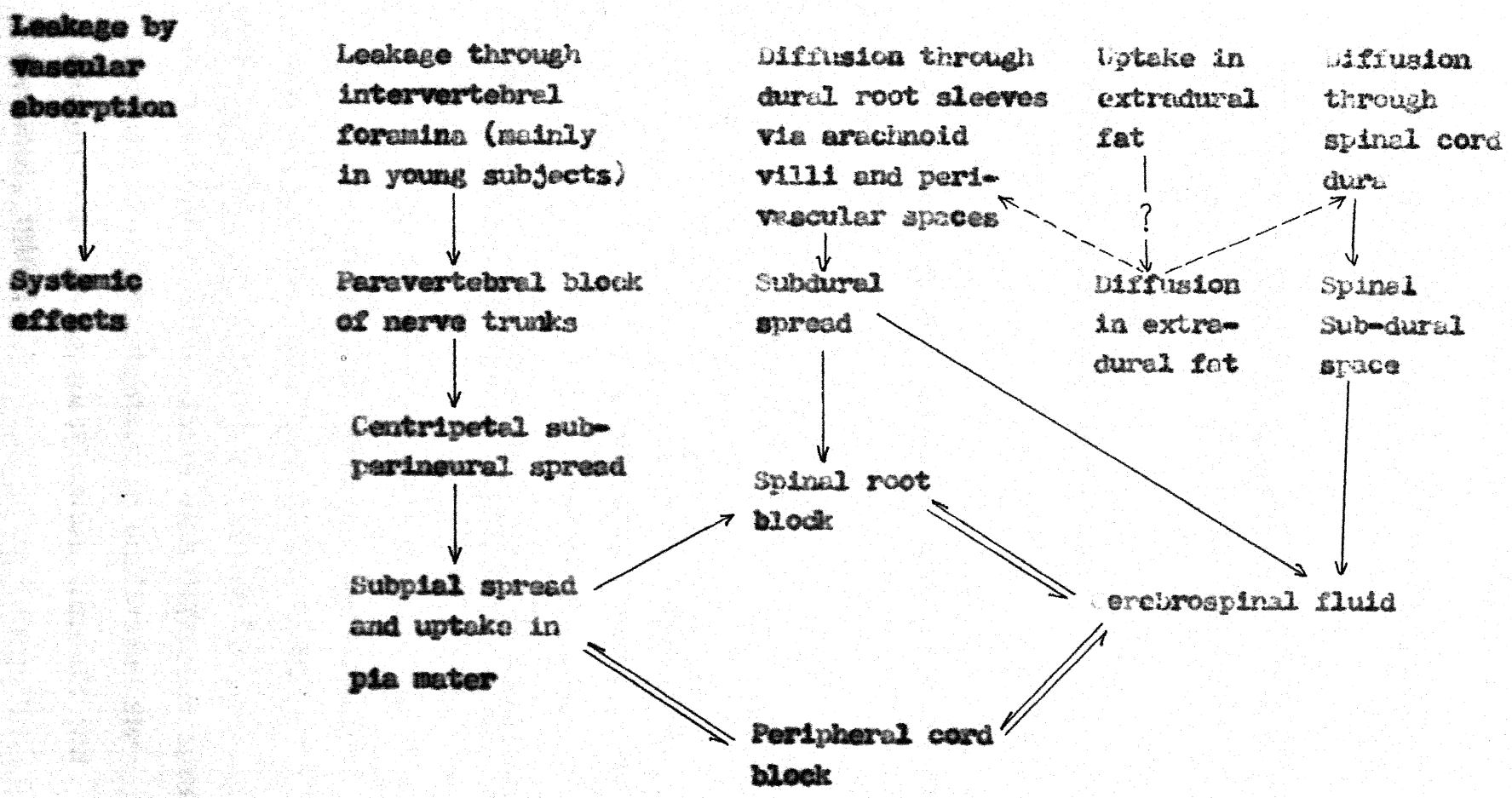
Sicard and Forestair (1921) injected india ink and lipoidal suspension in an attempt to study the study the site of action of analgesic solution and noted that these solutions tracked along with the intervertebral foramina and could be traced in the regional lymph glands 10 days after the injection. Odom, (1936) also confirmed that the leakage of solutions through each intervertebral foramen was constant and felt that analgesic solution acted at the paravertebral level. Bromage (1957) has produced a following working hypothesis reconciling all the clinical and experimental evidences available for the mode of action of epidural anaesthesia, as shown in the coming chart.

Lund (1961) observed greater dispersion of radio-opaque solutions in the older age group, with less leakage of solution through intervertebral formina. He attributed this to lesser patency of the foramina. Erdemir et al., (1965) observed that even the weakest correlation does not exist between the height of the patient and the dispersion of solution.

The factors controlling the height of epidural analgesia may be summarised as the site of injection, volume of solution, position of patient

The fate of an extradural injection

Longitudinal spread in Extradural space (Volume dependent)



after injection, concentration of solution, pregnancy and intra-abdominal tumours. There is an exaggerated spread of epidural anaesthesia in arteriosclerotic patients. (Bromage, 1962).

The cephalad border of analgesia was determined by Urban (1973), 0.75 to 4 hours following induction of spinal or lumbar epidural anaesthesia. Levels thus obtained followed a straight line best described by the skin intercept of a transverse section through the trunk. There was no difference between spinal and epidural anaesthesia in this regard.

Site of Action -

As regards the site of action of extra durally injected solution, it acts in three ways. Firstly, by passing through the duramater, secondly, by affecting the nerves in the paravertebral spaces and thirdly,at the ink-cuff zones, where dura thins out to become perineurium, permitting the passage of crystalloid molecules and Colloidal carbon (Woollam and Millen, 1953). Frumin et al., (1953) have demonstrated extradural local analgesic in the cerebro-spinal fluid at a different level. Whether this concentration is sufficient for analgesia or not is questionable (Sarnoff and Arrowood, 1946).

Opiates as epidural analgesics -

Post operative pain following abdominal and thoracic operations was relieved by lignocaine, with the disadvantage of tachyphylaxis. Later long acting drug Bupivacaine was used to give analgesia for 8-12 hours (Moore, 1975; Cronin and Davies 1976). Later opiates were used as epidural analgesics for chronic as well as acute pain of post operative period. The drugs used are Morphine 2-3 mg. (Behar, 1979; Bapat, 1979); Pethidine 100 mg. (Cousins et al., 1979) and Fentanyl 0.1 mg. (Wolfe et al., 1979). Behar et al., (1979) injected 2 mg. of morphine for acute or chronic pain, onset of action was 2-3 minutes and effect lasted from 6-24 hours. Bapat (1979) found the onset to be 5 minutes in acute cases and $1\frac{1}{4}$ - 2 minutes in chronic cases. The duration of action was 20-40 hours to 15 days in chronic cases. Husemeyer et al., (1979) found that 2 mg. of epidural morphine was ineffective to provide adequate analgesia in labour. Chayen et al., (1980) tried epidural morphine after caesarean section. They reported that relief of pain was sufficient to substitute surgical anaesthesia.

In the experiment of Gupta et al., (1980) onset remained the same, as in Behar series but the duration was found to be 6 hours to 7 days.

while amputees got permanent relief, with the same dosage of epidural morphine. In the series of Jean et al., (1980) pain relief lasted for 390 to 1205 minutes after 2 mg. of morphine. Johnston et al., (1980) pointed out the duration to be 3-50 hours in the cases of multiple fractured ribs. McClure et al., (1980) compared the results of 2-5 mg. morphine with a placebo injection in post operative period. After 20 minutes of injection, the placebo group, as a whole, had a satisfactorily significant reduction in the mean pain score. Few of the placebo group patients asked for further injections of drug, as they felt pain after 20 minutes. Scott and McClure, (1979) found 2 mg. morphine in 10 ml. saline to be inadequate to provide analgesia in the immediate post operative period, but usually gave good results on the day following surgery.

Rapat et al.- 2 mg. morphine epidurally.

Type of pain	No.of cases	Pain relief		
		Onset (mts.)	Degree	Duration
Chronic	7	$\frac{1}{4}$ - 2	100%	10days-3 cases 15days-3 cases 24 hrs.-1 case
Acute on chronic (gengrene)	1	2	75%	48 hours.
Acute (Post-operative)	4	5	100%	20-40 hours.
Acute (Obstetric)	5	5	50-75%	3-4 hours.

Observer	Onset (mts.)	Peak (mts.)	Duration
Morphine - 2 mg.			
Behar et al.	2-3	10-15	6-24 hrs.
Bapat et al.	acute - 5	-	3-24 hrs.
	chronic-1¼ -2	-	1-15 days.
Gupta et al.	2-3	-	6-7 hrs. - 7 days
Joan et al.	-	-	390-1205 mts. mean 733 mts.
Johnston et al.	2-3	-	3-50 hrs. mean 6-67 hrs.
Pethidine 100 mg.			
Cousins et al.	5	10-20	4.5-20 hrs. mean 6 hrs.
Fentanyl .1 mg.			
Wolfe et al.	4-10	20	200-240 mts.

Extradural morphine has been reported to produce analgesia within 5 minutes (Behar et al., 1979; Magora et al., 1980). The effect of morphine sulphate on single unit activities of various dorsal Rexed laminae was studied by Luke et al.,(1974) using an extracellular micro-electrode recording technique in decerebrate spinal cats. Intravenous morphine sulphate, 0.5, 1 and 2 mg./Kg. body weight supressed, in a dose related manner, spontaneous single unit activities in Rexed laminae 1 & 5, known to respond principally to noxious stimuli. It however did not effect spontaneous activities in lamina 4 and 5, known to respond to non-noxious

stimuli. Morphine and related compounds have significant effects on the spinal cord.

Animal experiments on cats by Kasaka et al., (1974) suggested that morphine causes selective suppression of Rexed laminae 1 and 5. Wang (1979) demonstrated that the response to nociceptive stimuli (flexor and crossed extensor reflex) was markedly depressed while the response to stretch (Knee and ankle jerks) was either not affected or slightly augmented by morphine sulphate.

Plasma concentrations of morphine, after intramuscular, extradural and intrathecal injections were studied by Chauvin et al., (1981). They concluded that morphine given extradurally has a higher rate of vascular absorption than morphine given intrathecally, the former being similar to that observed after intramuscular administration.

The radio-immune assay test showed that the opiate was present in the cerebro-spinal fluid after the epidural injection of morphine and it reached the peak value after about 35 minutes. Here the systemic concentration of morphine was negligible whereas its concentration in cerebro-spinal fluid was relatively high (Behar et al., 1979).

Chambers et al., (1981) introduced 10 mg. morphine in epidural space, before the onset of pain, by mixing it in 20 ml. of 0.5% bupivacaine and found better results when the morphine was given before the pain was present.

The commonly used preparations of morphine contain preservatives like chlorocresol, chlorobutanol and methyl hydroxy benzoate, giving an additional level of analgesia. Preparations containing preservative for epidural and intrathecal injections may cause paralysis (Craig, 1977).

Cousins et al., (1979), injected 100 mg. of pethidine hydrochloride, in 10 ml. of saline, epidurally. The pain relief started at 5th minute, with mean duration of action 6 hours, range 4.5-20 hours. Mather (1975) studied the blood concentration of pethidine after epidural injection which was similar to that following intramuscular injection.

Rutter et al., (1981) compared the results of morphine, pethidine and fentanyl using them in 2 mg., 50mg. and .1 mg. dosage respectively. They concluded the results, using a visual linear analogue; pethidine was found to be least effective, morphine longest acting and fentanyl had a relatively shorter duration of action. In all

patients there was a decrease in respiratory rate, but there was no depression of ventilation as judged by changes in $PaCo_2$.

Epidural fentenyl was first used by Wolfe et al., (1979) in the form of 0.1 mg. in 8 ml. 0.9% normal saline. Pain relief started in 4-10 minutes and lasted for 200-400 minutes, with a peak action in 20 minutes. No significant alteration in heart rate, blood pressure, respiratory rate or consciousness level was detectable. Baily and Smith (1980) used fentanyl with excellent results. Rutter et al., (1981) found poor results with 0.1 mg. fentanyl, with a duration of action of 2 hours. Nalda et al., (1981) used .25 mg. fentanyl with good results.

No literature is available on Fortwin given epidurally for post operative period.

Side effects - Morphine - In Rapat series, all the patients received 2 mg. morphine epidurally. Three patients of chronic pain did not pass urine for 12 hours. Reiz et al., (1980) reported the side effects of morphine chloride out of their experience of 1200 patients. They used 2 mg. morphine in 10 ml. normal saline. In the first 242 patients a commercial prepration containing sodium pyrosulphite 0.1 mg.

and sodium EDTA 0.1 mg. per 10 mg. morphine chloride was used. The remaining 958 patients were treated with a preservative free filtered solution.

The side effects as related to epidural morphine were :-

Side effects	No.	Percentage
Nausea & vomiting	204	17%
B.P.drop 20 mm of Hg.	24	2%
Itching (first 242 pts.)	36	15%
Itching (Next 958 pts.)	9	1%
Urinary retention	181	15%
Respiratory depression	1	.09%

Hales, (1980) reported pruritis in case of fractured rib, with 5 mg. morphine in 10 ml. normal saline. Pruritis was from nipple to knee and it disappeared with the disappearance of analgesia.

In the series of Andrews and Surendren, (1981), one patient developed respiratory depression. The patient was having obstructive jaundice. The respiratory rate was reduced to around 6-8 per minute, reversed by lethidron. One patient developed itching all over the body. Two patients had vomiting. Four patients complained urinary retention upto 18-24 hours following surgery. None of them needed

catheterization.

There are reports of respiratory depression and coma following epidural opioids, time of onset is from 45 minutes (Glynn, et al., 1979; Scott and McClure, 1979; Boas, 1980; Welch, 1981), to 4-6 hours (Christensen, 1980; Reiz and Westberg, 1980).

Glynn et al., (1979) administered 100 mg. of pethidine in two old patients, the onset of sedation and respiratory depression was approximately after 30 mimutes. Scott and McClure, (1979) found respiratory depression with 100 mg. of pethidine in two old patients, and required naloxone intravenously.

Wolfe and Nicholas, (1979) found complete absence of side-effects in their series. Ligander and Stenquist, (1981) have shown experimentally in cats that fentanyl .01-.05 mg. given extradurally abolished or substantially reduced the inhibitory reflex with a latent period of 5 minutes or less, thus producing paralytic ileus.

Mode of Action - Opiates act as agonists interacting with stereospecific saturable binding sites or receptors in the brain and other tissues. These

binding sites are widely and unevenly distributed throughout the central nervous system, with maximum concentration in limbic system, thalamus, striatus, hypothalamus, mid brain and spinal cord (Synder et al., 1974; Simon and Hiller, 1978). Affinity for the binding sites marks their potency. Met-enkephalin and leucine-enkephalin and other larger polypeptides isolated from brain and other tissues interact with opioid receptors producing similar but not identical pattern. Opioids decrease the release of acetylcholine from some peripheral and central cholinergic neurons, elevate brain acetylcholine level and antagonise the acetylcholine depleting effects of hemicholinium. (Domino and Wilson, 1973). In some preparations, morphine blocks the effect of 5 hydroxytryptamine but can also stimulate its release from gut. Chronic administration increases the turnover of 5 hydroxy-tryptamine in brain.

Specialized cell cultures are needed for the study of mode of action. Opiates decrease the activity of adenylate cyclase in such cultures. But whether the changes of cyclic AMP in neurons are related with actions of opiates is not established. Opiates can alter the release of a

number of neuro-transmitters. Transmembrane transport of Ca^{++} is affected leading to its depletion in brain, thereby relating the antagnonising effect of Ca^{++} (Way, 1978). Furthermore opiates suppress the activation of membrane-bound protein-kinase needed for phosphorylation of other membrane proteins, by calcium (Clouet et al., (1978); Schulman and Greengard, 1978). Any plus ion also effects the affinity of opiates for receptors. Its elevation reduces the affinity of binding of agonists while increasing that of antagonists (Synder, 1978).

Pharmacology of drugs -

MORPHINE - morphine is the principal alkaloid contained in opium, the dried powder derived from the milky exudate of the capsule of poppy (Papaver somniferum). The poppy juice being first referred by Theophrastus in 300 B.C. and Dioscorides in 60 A.D.. In 1807, Serturner, named morphine after Morpheus, the Greek God of dreams.

Morphine produces its major effects on the central nervous system and bowel. The therapeutic dose of morphine produces analgesia, drowsiness, changes in mood and mental clouding.

There is no loss of consciousness with selective relief of pain; other sensory modalities like touch, vibration, vision, hearing etc., are not affected. Continuous dull pain is relieved more than sharp intermittent pain. Morphine administration leads to central nervous system depression, causing analgesia, sleep, respiratory depression, depression of cough reflex. Central nervous system stimulation, produced by it, leads to vomiting, meiosis, hyperactive spinal cord reflexes, rarely convulsions. Changes of mood like euphoria and dysphoria are known to occur. Moreover morphine produces smooth muscle stimulation, causing gastro-intestinal muscle spasm (constipation), biliary tract spasm and renal tract spasm. The respiratory centre is depressed, leading to a reduction in the respiratory rate and minute volume. Respiratory depression is progressive with increasing dosage and is the principal toxic effect of overdose, after which the respiratory rate may fall to three per minute, the patient may become comatosed, hypotensive and cyanosed. The respiratory depression, coupled with pin-point pupils, is usually diagnostic of narcotic over-dose, though in extremes the pupils may dialate.

Morphine is poorly absorbed from the gastrointestinal tract because it is conjugated in the gut wall (Brunk and Delle, 1974). After given by injection, it is quite extensively taken up in the tissues, readily crosses the blood brain barrier and placenta to the foetus, producing respiratory depression. Having free OH groups, morphine is conjugated in the liver and the conjugated metabolites are rapidly excreted by the kidneys. The usual dose of morphine is 0.1-0.2 mg. per Kg. body weight, though more than this may be required in resistant individuals.

PETHIDINE- Pethidine was first synthesized in 1939 by Schaumann and Eisleb at the Hoechst Farbwerke in Germany in a search for an atropine substitute.

The structure of pethidine does not resemble that of morphine but its molecule conforms to the steric configuration of the opioids receptor, thereby having same mode of action as that of morphine. The principal difference being that both analgesia and side effects are of brief duration. The sedative and tranquillising effects are almost as good, and though the incidence of nausea, vomiting, dry mouth, hypotension and

dizziness is transiently higher than after morphine, the duration of these side-effects is brief (Dundee et al., 1965). Pethidine does not cause gastrointestinal tract spasm and meiosis. It causes dangerous interaction with monoamine oxidase inhibitors.

Pethidine raises the cerebro-spinal fluid pressure. It often relieves bronchial spasm. It causes spasm of the sphincter of Oddi, an effect counteracted by amyl nitrite, nitro-glycerine, adrenaline, and aminophylline. It reduces tone and amplitude of contraction of ureters.

It may release histamine from tissues, producing a typical triple response. It has a quinidine - like effect on myocardium and has been used to reduce the incidence of arrhythmias associated with cyclopropane anaesthesia. It may increase the incidence of post operative nausea and vomiting, an effect reduced by its combination with atropine or hyoscine (Dundee et al., 1964).

Pethidine is fairly rapidly broken down by liver, disease of which may retard its destruction. The principal product is nor-pethidine, excreted by kidney. Renal excretion can be increased

by forcing fluids and by making the urine more acid.

It is one tenth as potent as morphine and the dose is 1.5-2.0 mg./Kg. body weight.

PENTAZOCINE - was first described by Archer in 1962 and by Keats and Telford in 1964. Analgesic potency of 30 mg. equals to that of morphine 10 mg. and pethidine 75-100 mg. (Conaghan et al., 1966). Respiratory depression occurs equal to that of morphine and pethidine in equipotent doses. Hypertension may be produced (Keats and Terford, 1965).

The depression of pentazocine is not reversed by specific narotic antagonists, but by nikethamide ,and by methylphenidate (Doran and Burt, 1970) and by naloxone (Churchill, 1979). It raises the blood pressure. It is a very weak narcotic antagonist, being one fiftieth of the activity of nalorphine. It crosses the placenta less. It is of briefer duration of action than pethidine and less cumulative. Dose is 30-60 mg.

FENTANYL- It is a synthetic derivative of pethidine. It displays the typical spectrum of activity of the narcotic analgesics with the exception of having little hypnotic and sedative effects. The analgesic

action of a single intravenous dose of fentanyl will last for about 30 minutes, while the amount of fentanyl which is equianalgesic with 10 mg. morphine, is of the order of 0.2 mg. (Morrison Loan and Dundee, 1971). While lee and Atkinson (1977) mention that 0.05 mg. fentanyl has the analgesic potency of morphine 10 mg. or pethidine 100 mg.

Respiratory depression is marked, apnoea being common with doses in excess of 0.009 mg./Kg. body weight, can be antagonized by nalorphine and its congeners. Fantanyl has little effect on haemodynamic stability (Prys Roberts and Kelman, 1967; Tammisto et al., 1970) and it reduces both cerebral blood flow and cerebral oxygen consumption (Michenfelder and Theye, 1971). It is also a potent stimulator of vomiting centre.

Rigidity of the thoracic and abdominal muscles to an extent which makes inflation of the lungs difficult, has been reported after rapid intravenous injection of fentanyl (Corssen et al., 1964). This is presumably a manifestation of stimulation of spinal reflexes and, if it occurs, it can be abolished by the use of a muscle relaxant.

Fentanyl 0.1-0.6 mg. with droperidol 5 mg. produces neurolept anaesthesia. The combination of fentanyl 0.05 mg. and droperidol 2.5 mg. is available as thalamonal. Usual dose is 2 ml.

MATERIAL & METHODS

MATERIAL AND METHOD

The present study was carried out on 87 patients, admitted in various surgical wards of M.L.B.Medical College and Hospital, Jhansi during the year 1981-82.

The patients selected for study were those kept for operation by the departments of Surgery, Orthopaedics and Obstetrics and Gynaecology. The patients selected , were of ASA Grade 1, between the age group of 20 to 65 years. Prior to the operation the patients were fully examined in regard of their general condition, cardio-vascular and respiratory status. They were also subjected to a detailed nervous system examination, to rule out any possibility of neurological deficit. All the necessary investigations were carried out. Sensitivity test for lignocaine preceded the operation. In each case, one of the following drugs was injected epidurally:-

1. Morphine.
2. Pethidine.
3. Fortwin.
4. Fentanyl.

The total span of work comprised of two groups of patients.



TROLLEY FOR EPIDURAL CATHETERISATION

Group 1 - When surgery was also carried out with epidural technique for anaesthesia. Epidural canula used for this purpose was left in situ, to achieve post-operative analgesia by one of the above drugs introduced epidurally, as and when required.

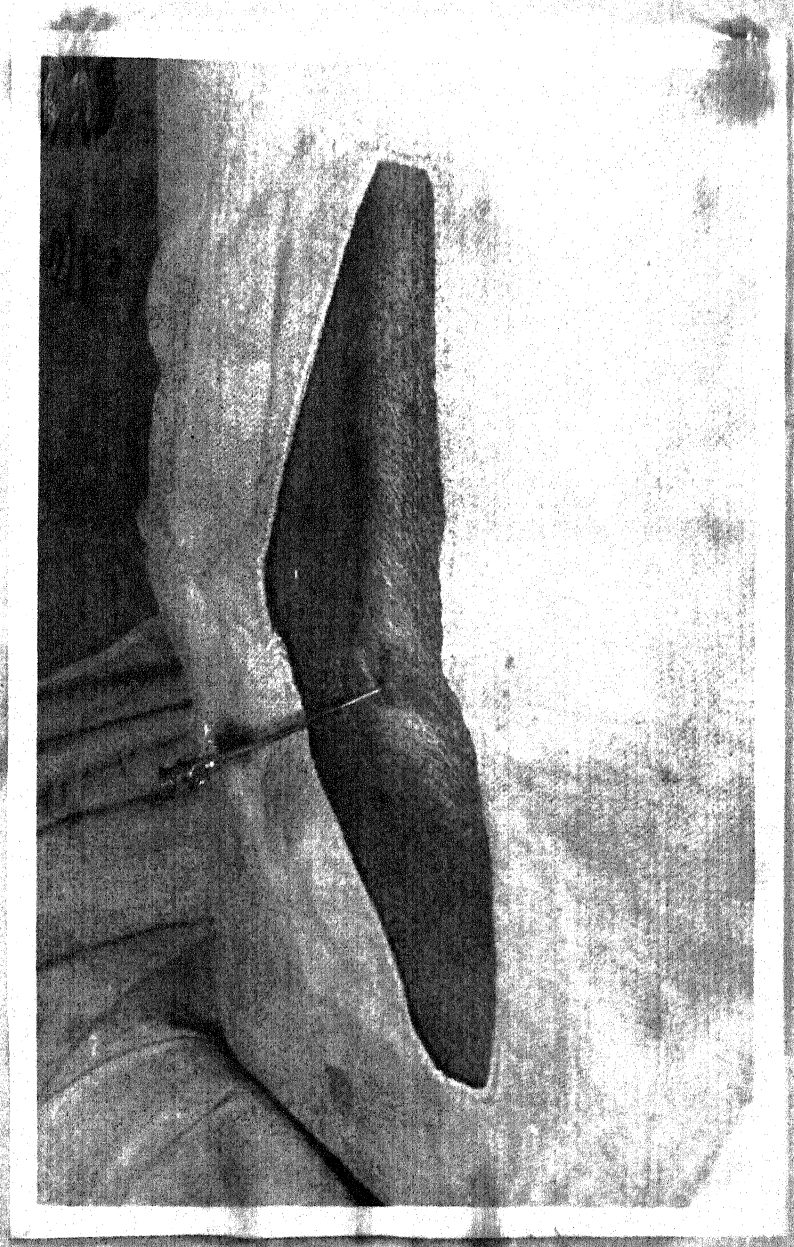
Group 2 - Cases operated upon under general anaesthesia with epidural canula placed for post-operative analgesia.

In the control group of patients pain relief, post-operatively, was tried with above mentioned pain killers given by conventional routes.

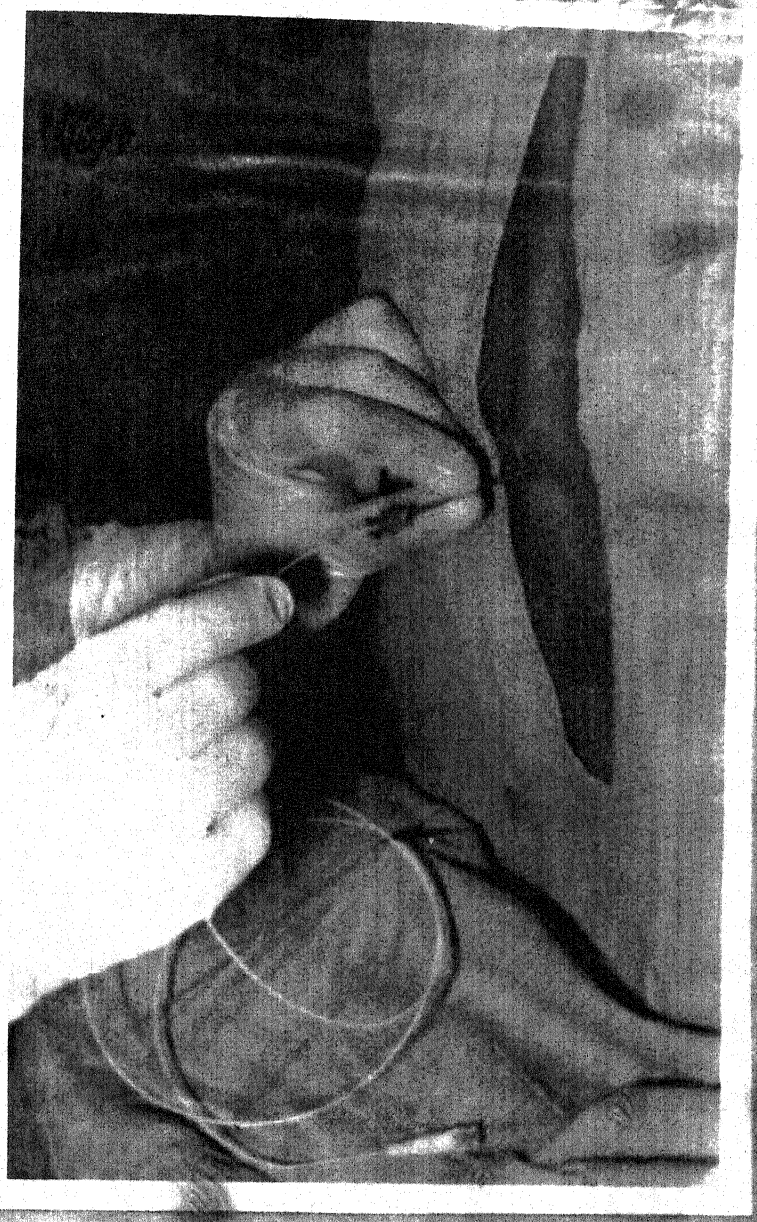
Epidural canula was left for 72 hours post-operatively, where morphine, pathidine and fortwin were used, while for 12 hours in cases of fentanyl.

The patients were distributed as follows depending upon the drug used and dose given.

Drug	No. of cases	Dose (in mg.)
Morphine	25	3
Pethidine	10	10
Pethidine	15	50
Fortwin	10	7.5
Fortwin	15	15
Fentanyl	12	0.1

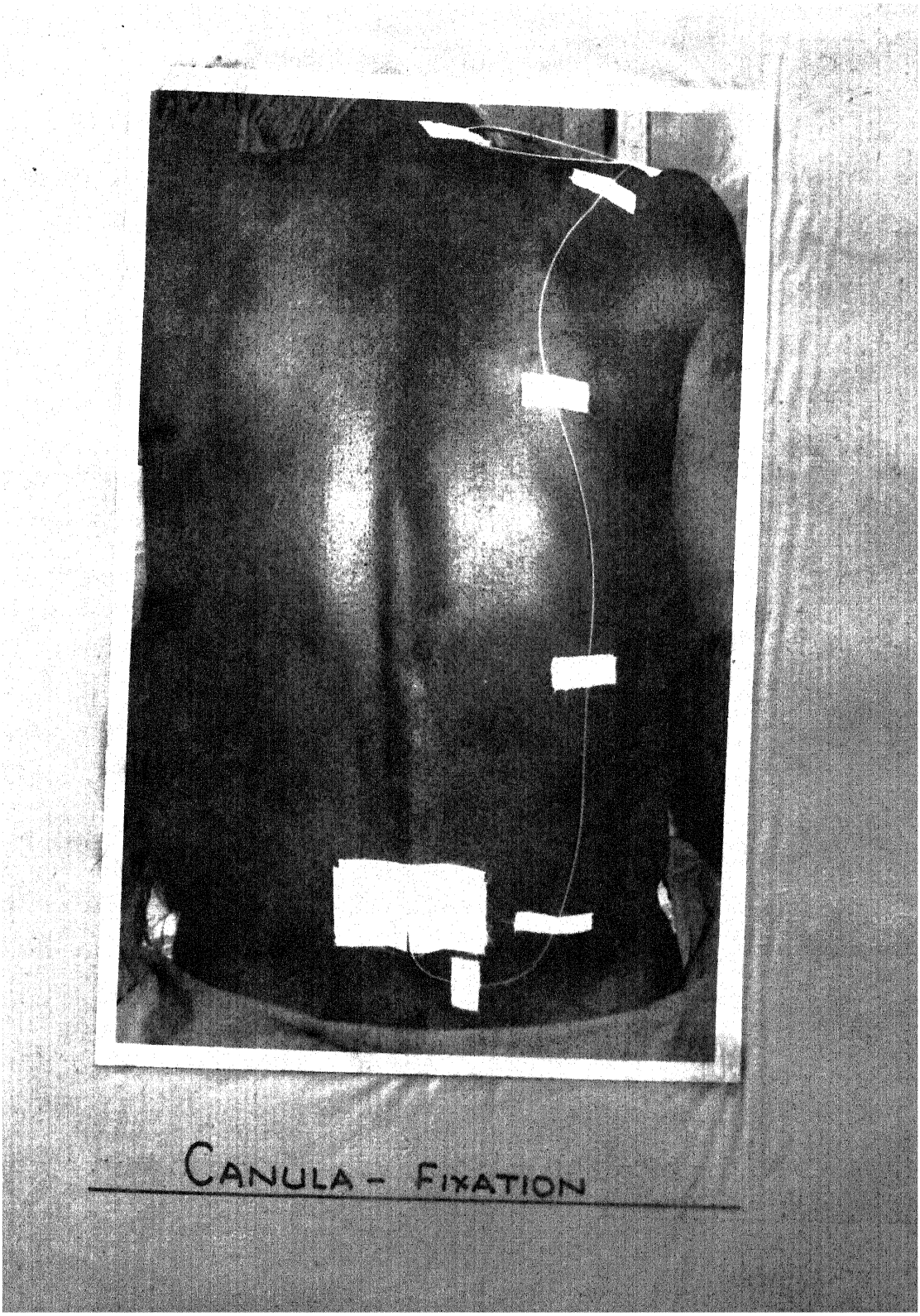


TUOHY NEEDLE IN EPIDURAL SPACE



ADVANCING CANULA THROUGH TUOHY NEEDLE

The sub-cutaneous tissue and the supraspinous and interspinous ligaments were also anaesthetized with the same dilute anaesthetic, using a 22 gauge, 5 cm. needle. A small cruciate incision was made at the site, in the centre of which Tuohy needle was inserted for epidural puncture. This procedure was essential to avoid the kinking of canula, after removing the needle. Needle in the epidural space was marked by sudden loss of resistance, and permitting easy passage of air through syringe. No cerebro-spinal fluid or blood came out, when sucked back. Till the ligamentum flavum was pierced the bevel of needle was kept laterally and after that it was made to point upwards or downwards depending upon the site of operation. The patency of the canula was checked and the tip was inserted into the needle and advanced. Resistance was encountered when the distal end of the canula passed beyond the bevel of the needle. This was overcome with slight additional force. Once the point of canula was beyond the needle, it was advanced to about 5 cm.. The needle was gently removed, and the canula was fixed with leucoplast. The free end of the canula was fixed in front of the shoulder. The patient was made to lie down on his/her back.



CANULA - FIXATION

For group 1 patients, 1.5% lignocaine, 15-20 ml. was given through epidural camula for anaesthesia during operation. In the post-operative period, when the patient complained of pain, the selected drug was injected epidurally, procedure being repeated every time when patient felt pain. After 10-15 minutes of the injection, the pulse, blood pressure, respiratory rate, tidal volume and the level of analgesia were recorded. The patient was examined for any sensory or motor loss. Thirty to forty five minutes after it, again respiration, pulse and blood pressure were checked.

For group 2 patients, the camula was inserted and anchored in the same manner. No drug was used before or during the operation epidurally. Post-operative analgesia was obtained in the similar manner as noted above for the group 1 patients, by epidural injection of selected drug.

Response of the epidurally injected drug was judged according to the basis of obtained level of analgesia. The analgesia was assessed on subjective basis and its level was divided into three degrees, namely, excellent, fair and poor, depending upon the perception of pain by the patient. Those patients were put in the 'excellent'

response category, in whom no pain was perceived post-operatively. If patient felt very little or no pain relief, he was placed in the 'poor' response category. In between, came the 'fair' response category where the patient was able to tolerate the existing pain.

In the control group above mentioned drugs were introduced intramuscularly in the same dosage to compare the effects.

The epidural canula was removed, after 12 hours in case of fentanyl, and after 72 hours in cases of morphine, pethidine and fortwin, post-operatively. The posture adopted for removal of canula was similar to that during inserting the same. The canula was checked for breakage. The site was sealed with cotton, soaked in tincture benzoin.

OBSERVATIONS

OBSERVATIONS

The present work of " A clinical study of Epidural morphine, pethidine, fortwin, and fentanyl for post-operative analgesia" has been made on a series of 87 cases and the following observations have been made.

Table No. 1

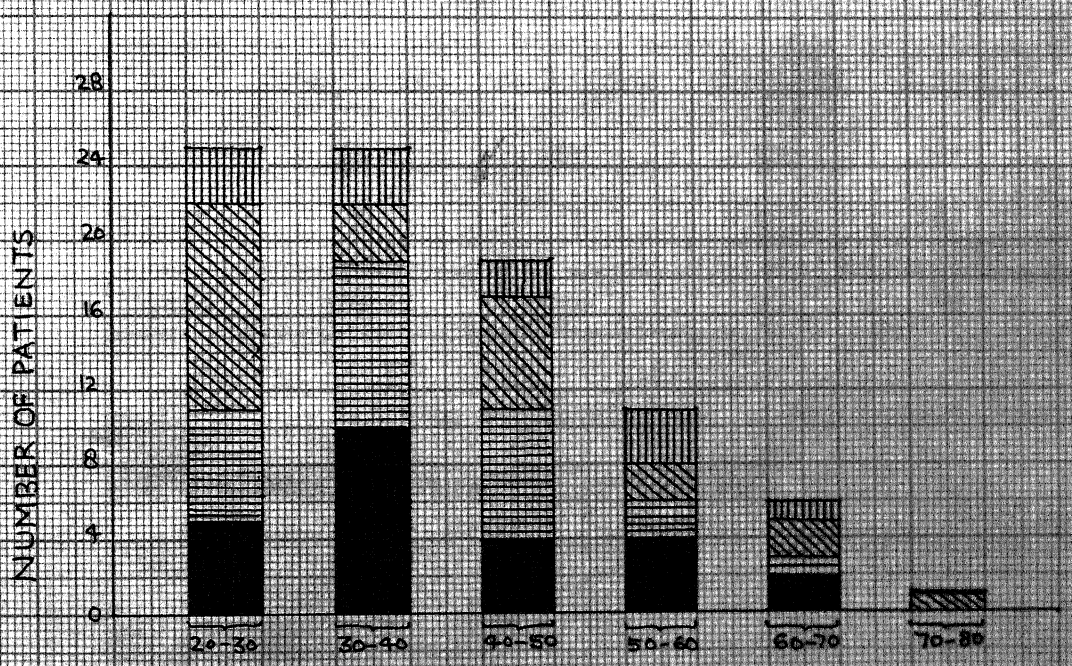
Age Incidence -

Table showing age-wise distribution of cases.

Age in years	Morphine	Pethidine	Fortwin	Fentanyl	Total	Percentage
20-30	5	6	11	3	25	28.73%
30-40	10	9	3	3	25	28.73%
40-50	4	7	6	2	19	21.83%
50-60	4	2	2	3	11	12.64%
60-70	2	1	2	1	6	6.89%
70-80	-	-	1	-	1	1.15%
Total	25	25	25	12	87	

The maximum number of cases studied, were in age group of 20-30 years, and 30-40 years (28.73%) each and the minimum number of cases were in the age group of 70-80 years (1.15%).

AGE-WISE DISTRIBUTION OF CASES



= MORPHINE

= PETHEDINE

= FORTWIN

= FENTANYL

SCALE - 1 BIG SQUARE = 4 CASES.

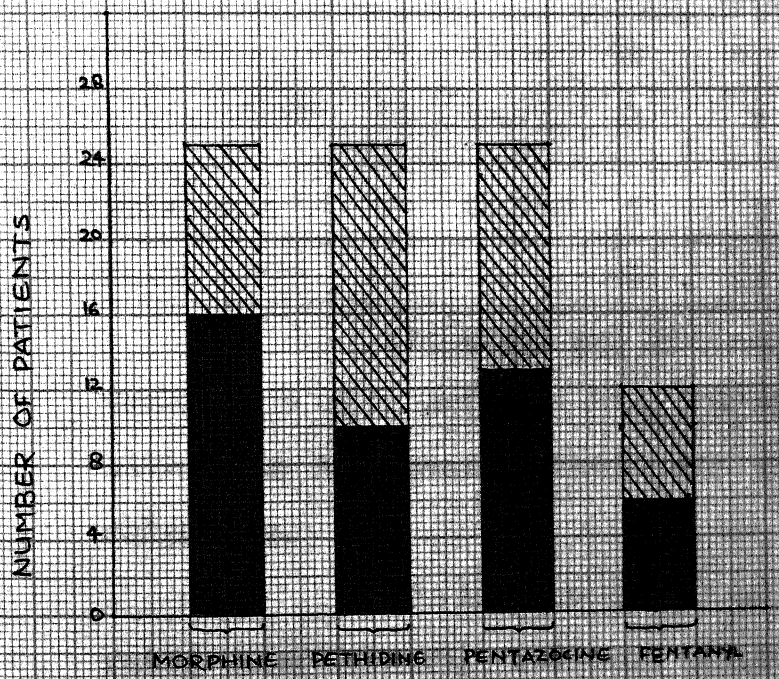
Table No. 2

Sex Distribution:

Table showing sex-wise distribution of the patients in each group -

Sex	Morphine	Pethidine	Fortwin	Fentanyl	Total
Male	16	10	13	6	45
Female	9	15	12	6	42
Total	25	25	25	12	87

The cases studied in the series included both sexes. Males predominated being about 52%.



SEX-WISE DISTRIBUTION OF CASES

▨ = FEMALES

■ = MALES

SCALE = 1 BIG SQUARE = 4 CASES.

Table No. 3

Table showing anaesthetic technique used for surgery and epidural analgesic drugs given post-operatively.

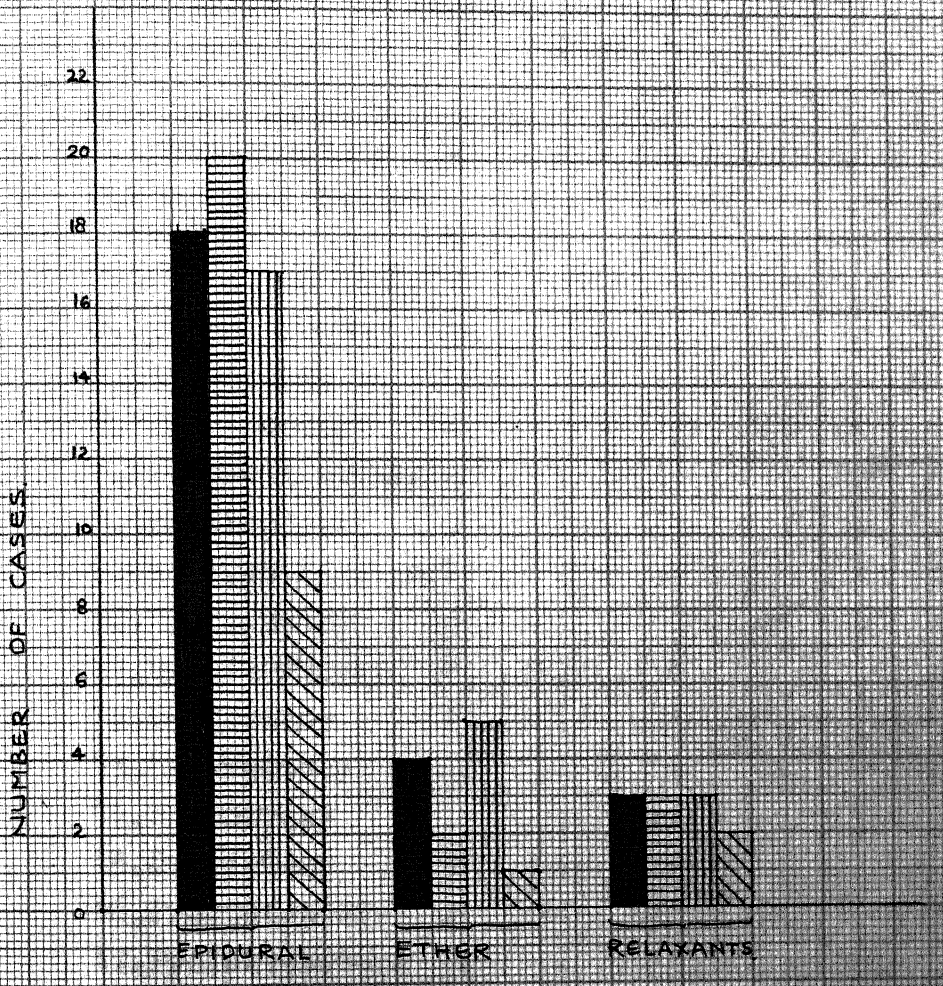
Anaesthetic technique	Total	Percentage	Drugs used for postoperative analgesia			
			Morphine	Pethidine	Fortwin	Fentanyl
Epidural	64	73.56%	18	20	17	9
(G.A.)Ether	12	13.79%	4	2	5	1
(G.A.) Relaxants	11	12.64%	3	3	3	2
Total	87		25	25	25	12

The cases got operated under the above techniques of anaesthesia viz. Epidural, General anaesthesia with ether and General anaesthesia supplemented with relaxants.

The maximum number of the cases were operated under epidural analgesia (73.56%). The postoperative analgesic used was given through the same canula in the post-operative period when the pain started.

In the cases, where operation was carried out under General anaesthesia, the post-operative analgesia was provided by injecting analgesic drugs epidurally. The maximum number of cases receiving post-operative analgesia were with epidural morphine(28%).

Fentanyl was used in minimum number of cases for extending post-operative analgesia.



ANAESTHETIC TECHNIQUE USED FOR SURGERY AND EPIDURAL ANALGESICS GIVEN POST-OPERATIVELY.

= MORPHINE

= PETHIDINE

= FORTWIN

= FENTANYL

SCALE - 1 BIG SQUARE = 2 CASES.

Table No. 4

Table showing types and number of surgical operations.

Operations	Total	Mor-phine	Pethidine in mg.		Fortwin in mg.		Fentanyl
			10	50	7.5	15	
1.Appendicectomy	4	2	-	1	-	-	1
2.Abdominal hysterectomy	3	1	2	-	-	-	-
3.Amputation penis	1	-	-	-	-	1	-
4.Cystolithotomy	4	1	-	1	-	1	1
5.Debridement	4	1	-	-	2	1	-
6.Fistulectomy	4	1	1	1	-	1	-
7.Fothergil repair	5	1	-	2	1	-	1
8.Graciloplasty	2	-	-	2	-	-	-
9.Haemorrhoidectomy	6	1	-	2	2	1	-
10.Hysterotomy	12	3	2	2	1	2	2
11.Herniorrhaphy	4	2	2	-	-	-	-
12.Laparotomy	7	1	1	-	2	2	1
13.Nephrectomy	2	1	-	-	-	-	1
14.Nephropexy	1	-	-	-	-	-	1
15.Ovariotomy	2	-	-	1	1	-	-
16.Prostatectomy	9	3	1	-	1	2	2
17.Pyelolithotomy	5	2	-	1	-	1	1
18.Saucerization	2	-	-	1	-	1	-
19.Sequestrectomy	2	1	-	-	-	1	-
20.Skin grafting	1	1	-	-	-	-	-
21.Vaginal hysterectomy	6	2	1	1	-	1	1
22.Vagotomy with gastrojejunostomy	1	1	-	-	-	-	-
Total		25	10	15	10	15	12

For post-operative analgesia the analgesic drugs were administered in 57 cases for different types of surgery. Maximum number of cases were of hysterotomy(12), while minimum were 1-1 case of skin grafting, amputation penis, vagotomy with gastro-jejunostomy and nephropexy.

Table No. 5

Table showing duration of analgesia after first dose of analgesic given epidurally.

Duration in hours	Morphine 3 mg.		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5 mg.		Fortwin 15 mg.		Fentanyl 0.1 mg.	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
0-10	4	16%	9	90%	5	33.3%	9	90%	1	6.66%	12	100%
10-20	17	68%	1	10%	6	40%	1	10%	8	53.3%	-	-
20-30	1	4%	-	-	-	-	-	-	1	6.66%	-	-
30-40	-	-	-	-	-	-	-	-	-	-	-	-
40-50	-	-	-	-	-	-	-	-	-	-	-	-
50-60	-	-	-	-	-	-	-	-	-	-	-	-
60-70	-	-	-	-	-	-	-	-	-	-	-	-
70-80	3	12%	-	-	4	26.6%	-	-	5	33.3%	-	-
Total	25		10		15		10		15		12	

The onset of analgesia was about 10 minutes.

Morphine (3 mg.):- 68% of cases had complete analgesia for 20-30 hours and 12% cases needed no repetetion of the analgesic for more than 72 hours, which we actually had made our target.

Pethidine (10 mg.):- In this series of 10 cases we did not get analgesia for more than 10-15 hours in any case, the onset being almost similar to that of morphine.

Fortwin (7.5 mg):- In this series of 10 cases analgesia could not be obtained for more than 10-15 hours.

Fortwin (15 mg.):- In yet another group of 15 cases where 15 mg. fortwin was given epidurally, there was analgesia for more than 72 hours in 33.3% cases and in the rest analgesia varying from 10-30 hours.

Fentanyl (0.1 mg.):- We did not observe post-operative analgesia for more than 2-3½ hours in all the 12 cases, which were given epidural fentanyl.

There has been no achievement of analgesia in one case each with morphine, 50 mg. pethidine and 15 mg. fortwin and hence the technique of extending post-operative analgesia with this procedure was abandoned in these patients.

Table No.6

Table showing total duration of analgesia after the epidural administration of second dose of the analgesics-

Duration in hours	Morphine 3 mg.		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5mg.		Fortwin 15 mg.		Fentanyl 0.1 mg.	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
0-10	-	-	-	-	-	-	-	-	-	-	12	100%
10-20	2	9.5%	9	90%	1	10%	9	90%	-	-	-	-
20-30	10	47.6%	1	10%	3	30%	1	10%	1	11.1%	-	-
30-40	4	19.5%	-	-	4	40%	-	-	6	66.6%	-	-
40-50	1	4.76%	-	-	-	-	-	-	-	-	-	-
50-60	-	-	-	-	-	-	-	-	-	-	-	-
60-70	-	-	-	-	-	-	-	-	-	-	-	-
70-80	4	19.5%	-	-	2	20%	-	-	2	22.2%	-	-
Total	21		10		10		10		9		12	

The second dose of the drug was given when the patient started feeling pain again.

Morphine: Analgesia for more than 72 hours was achieved in 19.5% of the remaining cases, where as most of the cases had complete pain relief for about 30-40 hours.

Pethidine (10 mg.): Showed only slight improvement in pain relief which persisted for about 20-25 hours.

Pethidine (30 mg.): The administration of the second dose of the drug further provided total pain relief for more than 72 hours to another 20% of the remaining cases. About 40% of the cases had post-operatively, got pain relief for more than 30-40 hours.

Fortwin (7.5 mg.): The second dose of the drug did not show much improvement in the duration of analgesia as the table shows analgesia for only 10-20 hours in about 90% cases.

Fortwin (15 mg.): With the introduction of the second dose of 15 mg. fortwin we observe analgesia for more than 72 hours in another 22.2% cases. Majority of cases (66.6%) had pain relief for more than 30 hours.

Fentanyl: Even the administration of second dose of the drug did not give any significant post-operative analgesia accounting any case. Further provision of analgesia was abandoned to the case with this drug and they were given other analgesic by the conventional route.

Table No. 7

Table showing total duration of analgesia after the administration of IIIrd dose of the analgesics given epidurally.

Duration in hours	Morphine		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5mg.		Fortwin 15 mg.	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
0-10	-	-	-	-	-	-	-	-	-	-
10-20	-	-	-	-	-	-	-	-	-	-
20-30	-	-	3	30%	-	-	4	40%	-	-
30-40	5	29.4%	7	70%	1	12.5%	5	50%	1	14.3%
40-50	5	29.4%	-	-	3	37.5%	1	10%	-	-
50-60	1	5.8%	-	-	-	-	-	-	1	14.3%
60-70	-	-	-	-	-	-	-	-	-	-
70-80	6	35.3%	-	-	4	50%	-	-	5	71.4%
Total	17		10		8		10		7	

Morphine(3mg.): The administration of third dose further gave complete relief to yet another 35.3% of remaining cases. The duration of analgesia in other patients was also for more than 50-60 hours.

Pethidine(10 mg.): Even the administration of the third dose did not give complete pain relief to the majority of cases for more than 30-40 hours.

Pethidine (50 mg.): About 50% of the remaining cases got post-operative pain relief for more than 72 hours after the third dose. Rest of the cases had pain relief

for periods ranging from 40-50 hours.

Fortwin (7.5 mg.): There was pain relief for only about 30-40 hours with the administration of third dose of the drug. Fortwin (15 mg.): gave complete relief from post-operative discomfort to about 71.4% cases. There was pain relief in other cases also for a considerable period of 50-60 hours.

Fentanyl : The third dose was not administered to the patients of this group as no analgesia was achieved worth consideration in any case.

Table No. 8

Table showing total duration of analgesia after the administration of fourth dose of analgesics given epidurally -

Duration in hours	Morphine		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5mg.		Fortwin 15mg.	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
0-10	-	-	-	-	-	-	-	-	-	-
10-20	-	-	-	-	-	-	-	-	-	-
20-30	-	-	-	-	-	-	-	-	-	-
30-40	-	-	4	40%	-	-	2	20%	-	-
40-50	2	18.2%	5	50%	1	25%	6	60%	-	-
50-60	3	27.3%	-	-	1	25%	-	-	-	-
60-70	1	9.09%	-	-	-	-	-	-	-	-
70-80	5	45.4%	1	10%	2	50%	2	20%	2	100%
Total	11		10		4		10		2	

Morphine: 11 out of 25 cases in this series which did not have complete post-operative pain relief for more than 72 hours, have yet been given the fourth dose of the drug. Now about 45.4% of the cases achieved the target. Remaining cases had pain relief for periods ranging from 50-60 hours.

Pethidine (10 mg.): This dose could extend pain relief to only 10% of the series for more than 72 hours. About 50% cases had relief of pain for about 40-50 hours.

Pethidine (50 mg.): About 50% of the remaining cases got pain relief measuring for more than 72 hours, others had for a period of 50-60 hours.

Fortwin (7.5 mg.): About 60% cases had post-operative well being for about 50-60 hours and 20% cases had full pain relief in the post-operative period for more than 72 hours.

Fortwin (15 mg.): The remaining 2 cases which did not have complete pain relief for more than 72 hours, achieved it, after the administration of fourth dose.

Table No. 9

Table showing total duration of analgesia after the administration of fifth dose of the analgesics given epidurally -

Duration in hours	Morphine		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5mg.		Fortwin 15mg.	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
0-10	-	-	-	-	-	-	-	-	-	-
10-20	-	-	-	-	-	-	-	-	-	-
20-30	-	-	-	-	-	-	-	-	-	-
30-40	-	-	-	-	-	-	-	-	-	-
40-50	-	-	3	33.3%	-	-	1	12.5%	-	-
50-60	-	-	5	55.5%	-	-	7	87.5%	-	-
60-70	-	-	-	-	-	-	-	-	-	-
70-80	6	100%	1	11.1%	2	100%	-	-	-	-
Total	6		9		2		8			

The administration of the fifth dose of the analgesic drug given epidurally, almost gave complete post-operative pain relief to about 100% cases with morphine, 50 mg. pethidine and 15 mg. fortwin.

There had been relief in post-operative pain for 50-60 hours even after the fifth dose with 10 mg. pethidine and 7.5 mg. fortwin.

Table No. 10

Table showing total duration of analgesia after the administration of sixth dose of analgesics given epidurally.

Duration in hours	Morphine		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5mg.		Fortwin 15mg.	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
0-10	-	-	-	-	-	-	-	-	-	-
10-20	-	-	-	-	-	-	-	-	-	-
20-30	-	-	-	-	-	-	-	-	-	-
30-40	-	-	-	-	-	-	-	-	-	-
40-50	-	-	-	-	-	-	-	-	-	-
50-60	-	-	-	-	-	-	-	-	-	-
60-70	-	-	-	-	-	-	-	-	-	-
70-80	-	-	8	100%	-	-	8	100%	-	-

The epidural administration of the sixth dose of the analgesics could provide post-operative analgesia to 100% cases with 10 mg. pethidine and 7.5 mg. fortwin.

Table No. 11

Cumulative duration of analgesia 72 hours after epidural morphine, pethidine and fortwin.

Drugs used	Ist dose		IInd dose		IIIrd dose		IVth dose		Vth dose		VIth dose	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
1.Morphine	3	12%	4	21%	6	54.1%	5	75%	5	100%	-	-
2.Pethidine 10 mg.	-	-	-	-	-	-	1	10%	1	20%	8	100%
3.Pethidine 50 mg.	4	26.6%	2	42.8%	4	71.4%	2	85.7%	2	100%	-	-
4.Fortwin 7.5 mg.	-	-	-	-	-	-	2	20%	-	-	8	100%
5.Fortwin 15 mg.	5	33.3%	2	50%	5	85.7%	2	100%	-	-	-	-

The above table shows the number of dosages which had to be given for achieving complete post-operative analgesia for 72 hours or more than that.

Morphine: We observe that with morphine we could get 100% results after the IVth dose. Even the first dose gave complete analgesia for the stipulated period to 12% cases. Majority had it after the fourth dose.

Pethidine (10 mg.): For the same period 1 case got after fourth dose, one case after the Vth dose and the remaining 6 cases after the sixth dose.

Pethidine (50 mg.): Provided analgesia for the period to about 72.4% cases after third dose. The first dose was sufficient for the purpose to about 26.6% cases where as 100% achievement was after the fifth dose.

Fortwin (7.5 mg.): 100% success was achieved after the sixth dose where as in 20% cases target could be had after the fourth dose.

Fortwin (15 mg.): 85.7% achievement was after the third dose, 53.3% being after the first dose and 100% after the fourth dose.

Table No. 12

Table showing mean dose requirement of epidural Morphine (3 mg.) for post-operative analgesia in different types of surgery.

Type of surgery	No.of doses administered						No.of cases	Mean dose requirement
	1	2	3	4	5	6		
Upper abdominal	-	-	-	1	2	-	3	4.6
Lower abdominal + pelvic	3	2	3	4	1	-	13	2.84
Perineal	-	-	1	-	1	-	2	4
Limb	-	2	1	-	-	-	3	2.33
Pelvic(female)	-	-	-	1	2	-	3	4.6

3 mg. morphine was administered epidurally for post-operative analgesia, in different types of surgery.

For the upper abdominal and the female pelvic organ surgery like fothergil repair and vaginal hysterectomy the mean dose requirement was 4.6 times.

2.84 was the mean dose requirement for the lower abdominal and pelvic surgery.

For the perineal and limb surgeries the mean doses administered were 2.84 and 4 respectively.

Table No. 13

Table showing mean dose requirement of pethidine(10 mg.) for post-operative analgesia, in different types of surgery.

Type of surgery	No.of doses administered						No.of cases	Mean dose requirement
	1	2	3	4	5	6		
Upper abdominal	-	-	-	-	-	-	-	-
Lower abdominal + pelvic	-	-	2	-	4	2	8	4.75
Perineal	-	-	-	-	1	-	4	5
Limb	-	-	-	-	-	-	-	-
Pelvic(Female)	-	-	-	-	-	1	1	6

Pethidine (10 mg.) was administered 4.75 times for lower abdominal and pelvic surgery.

For perineal surgery the mean dose requirement was 5 times.

Pethidine was given epidurally 6 times (Mean dose) for female pelvic surgery for post-operative analgesia.

Table No. 14

Table showing mean dose requirement of epidural pethidine (50 mg.) for post-operative analgesia in different types of surgery.

Type of surgery	No. of doses administered						No. of cases	Mean dose requirement
	1	2	3	4	5	6		
Upper abdominal	-	-	-	-	1	-	1	5
Lower abdominal + pelvic	1	1	2	1	-	-	5	2.6
Perineal	1	-	-	-	-	-	1	1
Limb	-	-	-	-	-	-	-	-
Pelvic(Female)	1	-	1	-	1	-	3	3

50 mg. pethidine was administered for post-operative analgesia 5 times for the upper abdominal surgery.

Mean dose requirement was 2.6 times for the lower abdominal surgery while for the perineal surgery it was administered only once.

For the female pelvic organ surgery it was administered 3 times.

Table No.15

Table showing mean dose requirements of epidural fortwin (7.5 mg.) for post-operative analgesia in different types of surgery.

Type of Surgery	No.of doses administered						No.of cases	Mean dose requirement
	1	2	3	4	5	6		
Upper abdominal	-	-	-	-	-	-	-	-
Lower abdominal +pelvic	-	-	-	1	4	-	5	4.8
Perineal	-	-	-	-	2	-	2	5
Limb	-	-	2	-	-	-	2	3
Pelvic(Female)	-	-	-	-	1	-	1	5

7.5 mg. fortwin was administered in 10 cases for post-operative analgesia. For lower abdominal and pelvic surgery the mean dose requirement was 4.8 times.

For perineal and female pelvic organ surgery it was administered 5 times while for the limb surgery it was administered 3 times.

Table No. 16

Table showing mean dose requirement of epidural fortwin (15 mg.) for post-operative analgesia in different types of surgery.

Type of Surgery	No. of doses administered						No. of cases	Mean dose requirement
	1	2	3	4	5	6		
Upper abdominal	-	-	-	-	-	-	-	-
Lower abdominal + pelvic	1	-	5	1	-	-	7	2.85
Perineal	2	-	-	-	-	-	2	1
Limb	2	1	-	-	-	-	3	1.33
Pelvic(Female)	-	-	1	1	-	-	2	3.5

15 mg. fortwin was administered epidurally for post-operative analgesia in 15 cases. In one case the response was poor hence 14 cases were studied.

For lower abdominal and pelvic surgery the mean dose requirement was 2.85 times. For perineal and limb surgery it was 1 and 1.33 times respectively.

For the female pelvic organ surgery the drug was administered 3.5 times.

Fentanyl had a shorter duration of action (about 2-3 hours).

Tables showing changes in pulse, systolic and distolic blood pressures in pre-operative and post-operative period (at the onset of pain before giving drug, 10 minutes and 30 minutes after giving drug), with different epidural analgesics.

Table No. 17

n = 25

Morphine (3 mg.):

	Pulse(per minute) Mean±S.D.	Systolic B.P. (mm of Hg.) Mean± S.D.	Distolic B.P. (mm of Hg.) Mean ±S.D.
1.Pre-operative values	79.6 ±6.076841	123.6 ±7.519574	74.8 ±5.8468453
2.Post-operative values			
(i)Values before giving drug	86.5 ±9.269843	130.1 ±7.0604532	74.3 ±5.2818557
(ii)Values 10 minutes after giving drug	84.9 ±9.36126 t=0.615	128.3 ±7.287935 t=0.841	74.2 ±5.3924391 t=0.066
(iii)Values 30 minutes after giving drug	82.4 ±7.797435 t=1.708	126.4 ±6.640481 t=0.191	73.9 ±4.8906032 t=0.279

Table No. 18

n 10

Pethidine (10 mg.):

	Pulse(per minute) Mean±S.D.	Systolic B.P. (mm of Hg.) Mean±S.D.	Diastolic B.P. (mm of Hg.) Mean±S.D.
1.Pre-operative values	75.8 ±6.264183	120.4 ±7.53923	72.4 ±3.9191835
2.Post-operative values			
(i)Before giving drug	84.6 ±6.636264	127.8 ±6.954135	72.2 ±3.7363083
(ii)10-15 minutes after giving drug	83.0 ±6.14817 t=0.559	125.8 ±6.415605 t=0.668	71.8 ±3.7363083 t=0.179
(iii)30 minutes after giving drug	80.4 ±5.782732 t=1.51	123.8 ±7.318469 t=1.25	71.6 ±3.4409301 t=0.375

Table No. 19

n = 15

Pethidine (50 mg.):

	Pulse(Per minute) Mean±S.D.	Systolic B.P. (mm of Hg.) Mean±S.D.	Diastolic B.P. (mm of Hg.) Mean±S.D.
1. Pre-operative values	77.3 ±5.4341512	119.8 ±7.77946	70.1 ±2.4278934
2. Post-operative values			
(i) Before giving drug	83.6 ±6.332982	126.5 ±7.135591	71.1 ±2.2941955
(ii) 10-15 minutes after giving drug	83.1 ±6.038487 t=0.222	125.4 ±7.173097 t=0.421	71.6 ±2.3457861 t=0.592
(iii) 30 minutes after giving drug	80.4 ±4.7721413 t=1.568	123.2 ±6.6653331 t=1.30	70.13 ±2.3002898 t=1.194

Table No. 20

n = 10

Fortwin (7.5 mg.):

	Pulse(per minute) Mean±S.D.	Systolic B.P. (mm of Hg.) Mean±S.D.	Diastolic B.P. (mm of Hg.) Mean±S.D.
1. Pre-operative values	78.6 ±5.141984	119.4 ±6.069596	73.4 ±4.386424
2. Post-operative values			
(i) Before giving drug	82.6 ±6.161168	126.6 ±7.851114	73.4 ±3.29528
(ii) 10-15 minutes after giving drug	80.8 ±6.764613 t=0.620	125.2 ±7.141498 t=0.416	73.0 ±3.0 t=0.173
(iii) 30 minutes after giving drug	79.6 ±5.3516352 t=0.772	122.8 ±7.493997 t=1.1	73.2 ±4.5782092 t=0.09

Table No. 21

n=15

Fortwin (15 mg.):

	Pulse(per minute) Mean±S.D.	Systolic B.P. (mm of Hg.) Mean±S.D.	Diastolic B.P. (mm of Hg.) Mean±S.D.
1. Pre-operative values	78.6 ±5.497878	122.4 ±8.966508	72.6 ±3.0702877
2. Post-operative values			
(i) Before giving drug	85.2 ±7.476095	129.2 ±7.858753	73.3 ±3.4578412
(ii) 10-15 minutes after giving drug	84.7 ±7.492883 t=0.183	128.2 ±7.668811 t=0.352	73.2 ±2.9484 t=0.065
(iii) 30 minutes after giving drug	81.6 ±7.012369 t=1.36	125.3 ±8.14596 t=1.33	73.1 ±4.7254629 t=0.135

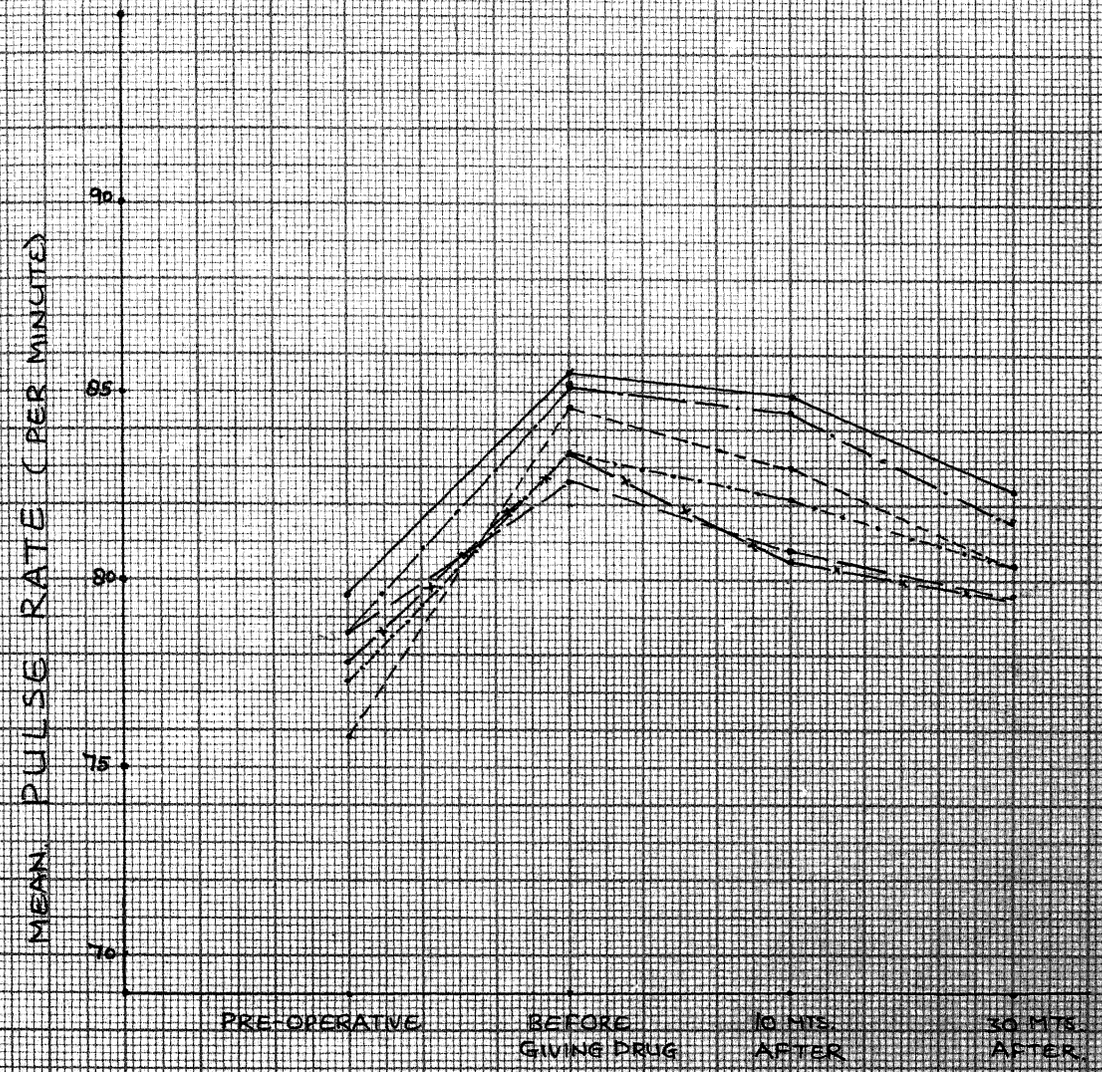
Table No. 22

Fentanyl (0.1 mg.): n = 12

	Pulse(Per minute) Mean±S.D.	Systolic B.P. (mm of Hg.) Mean±S.D.	Diastolic B.P. (mm of Hg.) Mean±S.D.
1.Pre-operative values	77.8 ±5.065955	121.5 ±7.963458	71.1 ±3.2109188
2.Post-operative values			
(i)Before giving drug	83.2 ±4.2879675	129.3 ±7.272551	71.6 ±3.2496153
(ii)10-15 minutes after giving drug	80.5 ±4.4429016 t=1.51	126.8 ±7.869138 t=0.809	71.3 ±3.0913858 t=0.232
(iii)30 minutes after giving drug	79.6 ±4.3924176 t=2.03*	124.6 ±8.741281 t=1.43	71.1 ±3.2109188 t=0.378

Morphine 3 mg., pethidine 10 mg., pethidine 50 mg., fortwin 7.5 mg., fortwin 15 mg. were administered for post-operative analgesia in different types of surgery. Pulse, systolic and diastolic blood pressures were recorded. No significant change was found in pulse and blood pressure after the administration of these drugs.

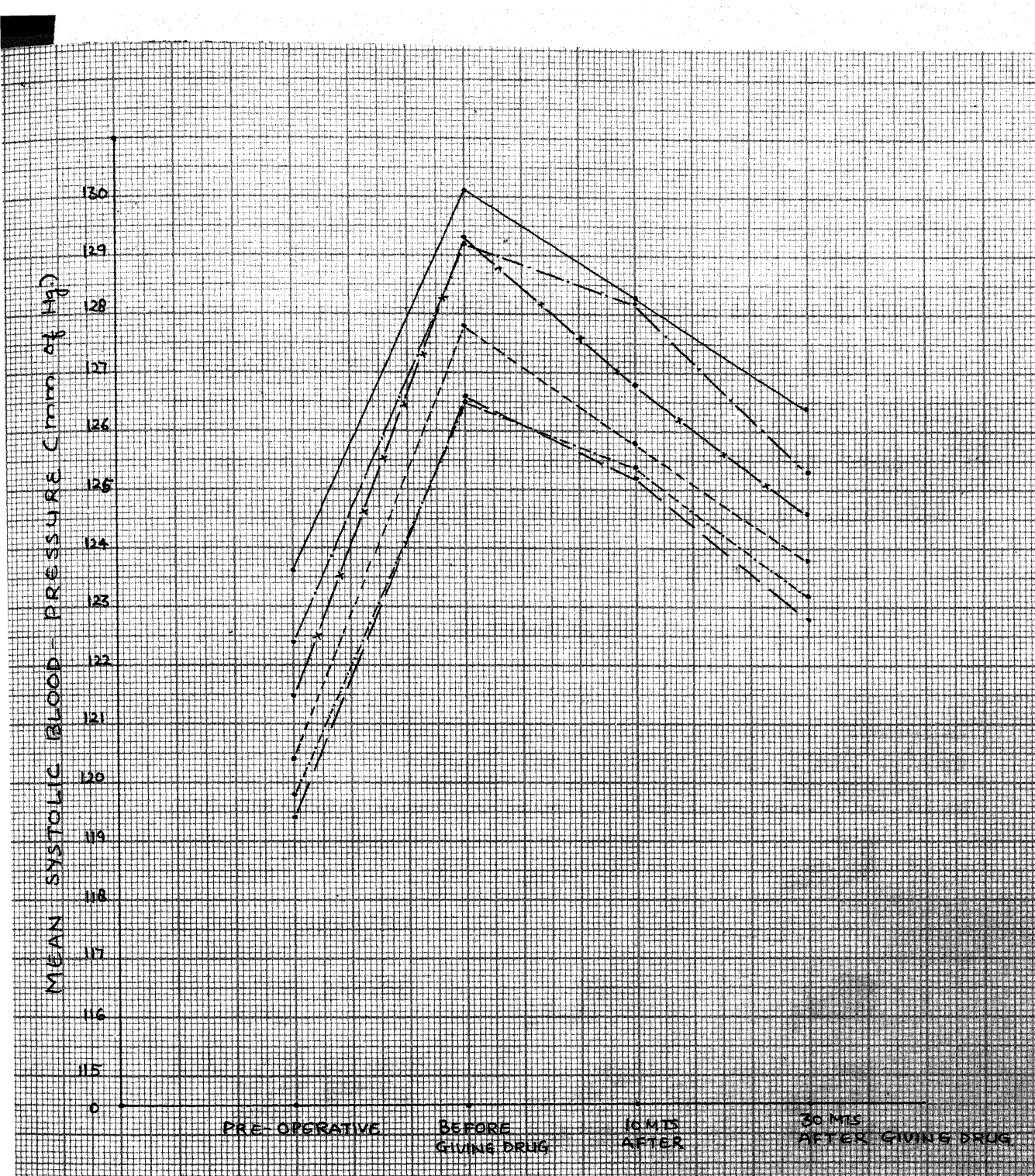
With fentanyl 0.1 mg. the significant change was seen in pulse value 30 minutes after the administration of drug. No significant change was observed in rest of the values.



MEAN CHANGES IN PULSE RATE

——— MORPHINE (3 mg)
– – – PETHIDINE (10 mg)
– – – PETHIDINE (50 mg)
– – – FORTWIN (7.5 mg)
– · – FORTWIN (15 mg)
– x – FENTANYL (0·1mg)

SCALE = 5 SMALL SQUARE = PULSE RATE 1/MINUTE.



MEAN CHANGES IN SYSTOLIC BLOOD PRESSURE

——— MORPHINE (5 mg.)
– – – PETHIDINE (100 mg.)
– – – PETHIDINE (50 mg.)
– · – · – CORTWIN (7.5 mg.)
– · – · – CORTWIN (15 mg.)
– · · – · · – FENTANYL (0.1 mg.)

SCALE – 1 BIG SQUARE = 1 mm. of Hg.

Tables showing changes in respiratory rate and tidal volume in pre-operative and post-operative periods (at the onset of pain, before giving drug, 10 minutes and 30 minutes after giving drug) with different epidural analgesics in upper abdominal and major lower abdominal surgery only.

Table No. 23

Morphine:

	No. of cases	Respiratory rate Mean±S.D.	Tidal volume Mean±S.D.
1. Pre-operative values	6	17.6 ± 1.107	360 ±39.58
2. Post-operative values			
(i) Before giving drug		24.8 ±1.95	235 ±16.07
(ii) 10-15 minutes after giving drug		21.8 ±2.41 t=2.38 *	306 ±22.11 t=2.61 *
(iii) 30 minutes after giving drug		18.8* ±0.998 t=6.85	321 ±39.08 t=0.813

The above table shows that there are significant changes in respiratory rate after the 10-15 minutes and 30 minutes dose of the drug whereas tidal volume is significantly altered with the dose after 10-15 minutes but in-significant after the 30 minutes dose.

Table No. 24

Pethidine (10 mg.):

	No. of cases	Respiratory rate Mean±S.D.	Tidal volume Mean±S.D.
1. Pre-operative values	3	18.3 ±4.72	386.6 ±12.47
2. Post-operative values			
(i) Before giving drug		24 ±0.816	350 ±16.33
(ii) 10-15 minutes after giving drug		23.3 ±0.943 t=0.972	356.6 ±3.96 t=0.682
(iii) 30 minutes after giving drug		22 ±1.63 t=1.90	350 ±16.32 t=1.03

Table No. 25

Pethidine (50 mg.):

	No.of cases	Respiratory rate Mean±S.D.	Tidal volume Mean±S.D.
1.Pre-operative values	2	16.5 ±0.5	415 ±15
2.Post-operative values			
(i)Before giving drug	2	20.5 ±0.5	370 ±20
(ii)10-15 minutes after giving drug		19 ±1 t=1.898	375 ±15 t=0.284
(iii)30 minutes after giving drug		17 ±2 t=2.413	380 ±10 t=0.633

With pethidine (10 mg.& 50 mg.) no significant change was found in respiratory rate and tidal volume 10-15 minutes and 30 minutes after the administration of drug in post-operative period. It was observed only in 3 cases of lower abdominal surgery with(10 mg.)pethidine (Table 24), and 4 cases with (50 mg.) pethidine (Table 25).

Table No. 26

Fortwin (7.5 mg.). n=3

	No.of cases	Respiratory rate Mean±S.D.	Tidal volume Mean±S.D.
1.Pre-operative values	3	17.3 ±0.943	403.3 ±12.47
2.Post-operative values			
(i)Before giving drug		20.6 ±1.06	366.6 ±4.71
(ii) 10-15 minutes after giving drug		19.6 ±0.945	373.3 ±4.71
		t= 1.21	t= 1.74
(iii)30 minutes after giving drug		19.0 ±0.816	376.6 ±5.19
		t= 0.519	t=2.47

Table No. 27

n=2

Fortwin (15 mg.):

	No.of cases	Respiratory rate Mean±S.D.	Tidal volume Mean±S.D.
1.Pre-operative values	2	18.5 ±1.5	400 ±30
2.Post-operative values			
(i)Before giving drug		23 ±1	320 ±30
(ii)10-15 minutes after giving drug		19 ±1 t=4	370 ±20 t=1.96
(iii)30 minutes after giving drug		19.5 ±0.5 t=4.43*	365 ±25 t=1.63

* Significant at - < 0.05

10 minutes and 30 minutes after the administration of 7.5 mg. fortwin we observed that there is no significant change in respiratory rate and tidal volume.

While with 15 mg. of fortwin the changes were significant 30 minutes after giving drug.

Table No. 28

Fentanyl (0.1 mg.):

	No.of cases	Respiratory rate Mean±S.D.	Tidal volume Mean±S.D.
1.Pre-operative values	2	18.5 ±0.5	405 ±15
2.Post-operative values			
(i)Before giving drug		26.5 ±1.5	260 ±10
(ii)10-15 minutes after giving drug		21 ±1 t=4.31 *	335 ±15 t=3.88 *
(iii)30 minutes after giving drug		17.5 ±0.5 t=8.05 *	340 ±20 t=5.06 *

Fentanyl 0.1 mg. was given in 2 cases of upper abdominal surgery. Significant changes in respiratory rate and tidal volume were seen 10-15 minutes and 30 minutes after the administration of drug.

Table No. 29

Table showing response of epidural analgesics.

Response of analgesics	Morphine		Pethidine 10 mg.		Pethidine 50 mg.		Fortwin 7.5mg.		Fortwin 15 mg.		Fentanyl	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
Excellent	14	56	3	30	9	60	3	30	10	66.6	8	66.6
Fair	10	40	7	70	5	33.3	7	70	4	26.6	4	33.3
Poor	1	4	-	-	1	6.7	-	-	1	6.7	-	-

The response of epidural analgesics was observed as follows:

Morphine : Morphine was administered in 25 cases, outof which the excellent response was observed in 14 cases (56%) fair in 10 cases (40%) and poor in 1 case(4%).

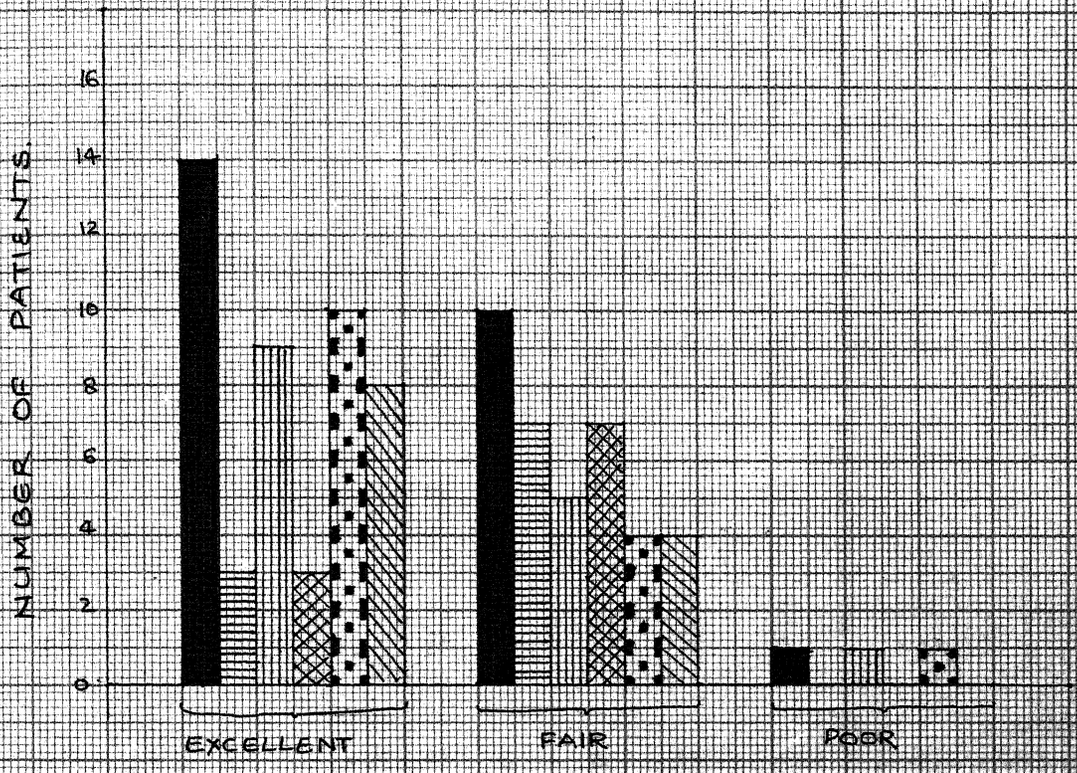
Pethidine (10mg.): Provided excellent response in 3 cases (30%), while fair response in 7 cases (70%).

Pethidine (50 mg.): The improvement in response was observed with 50 mg. pethidine. The excellent response was observed in 60% cases, fair response in 33.3% cases. 1 patient (6-7%) showed poor response.

Fortwin (7.5mg.): Provided excellent response in 30% cases while fair response in (70%) cases, in post-operative period.

Fortwin (15 mg.): The response was excellent in 66.6% cases; fair in 26.6% cases, while poor response was observed in only 1 case (6.7%).

Fentanyl : The analgesia was excellent in 66.6% cases but duration was very short. Fair response was observed in 33.3% cases.



RESPONSE OF EPIDURAL ANALGESICS

- MORPHINE (3mg)
- PETHIDINE (10mg)
- PETHIDINE (50mg)
- PORTWIN (7.5mg)
- PORTWIN (15 mg)
- FENTANYL (0.1 mg)

SCALE - 1 BIG SQUARE = 2 CASES

Table No. 39

Table showing side effects and complications of epidural analgesics, administered for post-operative pain relief.

S. No.	Side effects	Morphine 3mg.		Pethidine 10mg.		Pethidine 50mg.		Fortwin 7.5mg.		Fortwin 15mg.		Fentanyl 0.1mg.	
		No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
1.	Nausea	2	8.33%	1	10%	2	14.3%	-	-	1	14.3%	-	-
2.	Vomiting	3	12.6%	-	-	2	14.3%	-	-	-	-	1	8.33%
3.	Retention of urine	6	25%	-	-	3	21.4%	-	-	-	-	-	-
4.	Epigastric pain	-	-	1	10%	-	-	-	-	-	-	-	-
5.	Discomfort of cannula	8	33.3%	3	30%	7	50%	4	40%	5	35.7%	4	33.3%

Complications

Morphine: The side effects noticed were nausea, vomiting retention of urine and discomfort with canula.

Pethidine (10 mg.): Produced side effects like nausea and epigastric pain.

Pethidine (50 mg.): With the increase of dose the incidence of nausea, vomiting and retention of urine increased.

There was no considerable side effect noticed in the fortwin series of cases. Discomfort of canula was however complained by the majority of cases in all groups.

DISCUSSION

D I S C U S S I O N

The present series of " A clinical study of Epidural Morphine, Pethidine, Pentazocine and Fentanyl for post-operative analgesia " has been carried out on a series of 87 cases.

Provision of post-operative analgesia has been a great challenge to the anaesthesiologists. It involves pain-relief, general well bing and escape from the side-effects of post-anaesthetic complications. The post-operative pain, as well warrants the close watch on the part of the attending house staff and nurses.

The conventional methods of injecting the analgesics for post-operative analgesia become very cumbersome. There have to be repeated injections, in fairly high doses, which in their own turns, produce various side effects.

The identification by Synder of specific receptors which are sensitive to narcotics, in the substantia gelatinosa of posterior horn cells of spinal cord, in 1975, has opened up new concepts of treatment for pain and narcotic addiction. Opiate drugs are known to extract a direct anti-nociceptive influence on the spinal cord (Yaksh and Rudy, 1977, 1978). Drugs injected in the epidural space do reach the spinal cord finally

and this explains the ultimate action of epidurally injected morphine directly on opiate receptors.

Behar et al., (1979) used epidural morphine for the relief of pain. Further studies made by Majora et al.,(1980), also established encouraging results.

The present study has thus been taken under cover of the encouraging results by previous workers to establish a method for providing post-operative pain relief by epidural administration of various analgesic drugs. This provides pain relief for a much longer duration and the dose required is much less as compared to those needed for conventional routes.

The series comprised of patients of both sexes; no relationship has been found in respect of sex with the degree of pain relief.

Selection of cases and anaesthetic technique:

The cases studied in the present series consisted mostly of major surgeries, which needed post-operative pain relief for a comparatively longer period, say upto 70-80 hours.

The technique of anaesthesia had been epidural and general anaesthesia using inhalational anaesthetics and relaxants.

We administered epidural analgesics to most of the cases (73.56%) for surgery, so that we could introduce the analgesics drugs through the same canula in the post-operative period. This method avoided the necessity of introducing epidural canula in the post-operative period when the patient may be unco-operative.

13.79% cases got operated under general anaesthesia using an inhalational agent and 12.69% cases with relaxants. In these cases, the epidural canula was inserted first.

The administration of the analgesic drug was done as soon as the patient started feeling slight discomfort.

The drugs given by other conventional methods, if used at the start of pain, required larger doses and since the onset is longer, the patient is in agony for sometime. The preferrable timing in these cases has to be before the onset of pain which at times, becomes difficult to judge.

Dose of the drug:

The dosage of the drug, used for epidural administration, has been quite small. Morphine 3 mg., as against 10-15 mg. for other conventional

routes, was used. Pethidine was administered in two dosages viz 10 mg. and 50 mg.. Cousins et al.(1979) had used the same in the dosage of 100 mg.. We observed that as low a dose of 10 mg. provided pain relief to same extent. With the increase in dosage, the duration of analgesia was increased.

Pentazocine had been used in the dosages of 7.5 mg. and 15 mg.. The low dose has also been quite effective, but again similar to that of pethidine, the degree and duration of pain relief is enhanced with the increase in dosage.

Fentanyl was used in the dose of 0.1mg. which is far less than that given through other routes but provides effective pain relief, though of shorter duration.

The dose requirement has been dependent upon the site of surgery also. The upperabdominal surgeries needed more dosage repetitions than the perineal and limb surgeries. The female genital surgery cases, also needed more dosage of the drug. This has been true with all the drugs. (Tables 12-16).

Onset of action:

Onset of action with all the drugs viz. morphine, pethidine, pentazocine and fentanyl, given

epidurally, came out to be between 2-10 minutes. Our observations fully corroborate with the findings of Behar et al., (1979). In his series, with epidural morphine, the onset of action had been within 5 minutes. Cousins et al., (1979) used 100 mg. epidural pethidine and onset of action had been 5-6 minutes.

The onset of action of pain relief by intramuscular route, is fairly long and the patient has to be in agony for a longer period. Even the intravenous injection takes quite a few minutes for the onset of action. The rate of complications is much enhanced by these routes. The dose requirement is usually high. We observed that the epidural administration of the drugs, even in very small doses, had a quick onset.

Duration of action:

The stipulated period for provision of post-operative analgesia, in our series, had been for 72 hours or more than that. The first dose of the epidural analgesic was given just at the onset of slight discomfort in the post-operative period. The observations in our series are as follows:-

Morphine : We used the drug in 3 mg. dose. The duration of action, in 68% cases had been for 10-20 hours. It is in accordance with the findings of Jean et al.,(1980).

In their series of duration of analgesia was 12.2 hours in post-operative prostatectomy cases. 12% cases had pain relief for more than 72 hours. Thus we see that even as small a dose as that of 3 mg. is sufficient to provide pain relief for more than 3 days, whereas the requirement with other conventional routes must have been multiple pricks involving higher doses resulting into side-effects and addiction etc. This would also involve constant attendance on the part of junior doctors and the nursing staff. By extending pain relief through the epidural method, the required attendance on the part of the treating staff and anxiety on the part of the attendants of the patient become for less.

In the series of Behar et al., the duration of action had been 6-24 hours whereas in that of Bapat et al., it was 3-24 hours. These workers found that duration of action in acute cases was less than that in chronic cases.

In 47.6% cases the duration of analgesia lasted for 20-30 hours (Table, 6). Similar results were obtained by Andrews and Surendran (1980). In their series of 13 cases analgesia lasted for 24 hours in 10 cases.

The subsequent repetition of dosage increased the duration of analgesia. The second dose

was sufficient to produce analgesia for about 19.5% cases, whereas repetition of the drug to some patients was required even for 5 times, extending pain relief for the desired period (Tables 6-9).

The total dose required in different sites of operation, has also been variable and we observe that upper abdominal surgery cases needed epidural analgesic administration for 4.6 times (mean dose) (Table -12). The female pelvic operations needed 4.6 times dose-repetition (mean dose) for the same period (Table-12).

Pethidine (10 mg.): We used epidural pethidine in dosage of 10 mg. in a series of 10 cases. The duration of analgesia with this small dose has been less than 10 hours in 90% cases in the first instance (Table-6). For extending pain relief for more than 72 hours we had to give epidural pethidine in this dose for 6 times in most of the cases. 10 mg. pethidine is too small a dose but we find even this efficacious, though the repetitions of the drug are many.

Pethidine (50 mg.): With the increase in the dose of the drug, we observed that the degree and duration of analgesia increased considerably. 26.6% cases had analgesia for more than 72 hours even with the first

dose. About 85% had the same by fourth dose (Tables 6-8). Other workers like Cousins et al.,(1979) used 100 mg. epidural pethidine for pain relief. Simultaneously they measured CSF pethidine concentration. They observed onset of pain relief as 5 minutes which coincided with the presence of high concentration of pethidine in CSF (0.5-2 mg. per litre). Complete pain relief occured at 10-12 minutes (CSF level being 10-20 mg. per litre) and mean duration of action being 6 hours (range 4.5-20 hours).

We find, through our studies, that the dose requirement of pethidine even at 50 mg. is considerably effective for prolonged degree and duration of analgesia. If we employ higher dosage then the complications and side effects will definitely be increased (Table-13).

Rutter et al., (1981) compared the results of morphine, pethidine and fentanyl using 2 mg. , 50 mg. and 0.1 mg. respectively. They concluded the results by using a visual linear analogue. Pethidine was found to be least effective, morphine as longest acting and fentanyl had a relatively shorter duration of action.

In our series we found better results with pethidine 50 mg.. The fourth dose of the drug

achieved success in 85.7% cases, while the similar dose of morphine succeeded in 75% cases for giving pain relief for more than 72 hours (Table-11).

Pentazocine: Epidural pentazocine has not been used by other workerd, as post-operative analgesic, hence no literature is available on it. We used 7.5 mg. dose in 10 and 15 mg. dose in 15 patients.

The degree and duration of analgesia with this drug has also been quite encouraging. 15mg. dose of the drug was sufficient to extend pain relief for the desired period to about 33.3% cases (Table -5) which has been more than that with morphine or pethidine. 7.5 mg. pentazocine of course has not been effective for longer duration. In the majority of the cases, even 5 and 6 doses had to be given for achieving the results.

Maximum number of 4 doses were necessary in few to provide complete pain relief for more than 72 hours (Table -9).

Fentanyl: Epidural fentanyl was first used by Wolfe et al., (1979) in the form of 0.1 mg. in 8 ml. 0.9% normal saline. Pain relief started in 4-10 minutes and lasted for 200-400 minutes, with a peak action in 20 minutes. In our series of 12 cases who were given epidural fentanyl as post-operative analgesic,

series, in one case each, with 3 mg. morphine, 50 mg. pethidine and 15 mg. pentazocine which could be attributed to the faulty position of the catheter.

The response of the drug used had been very encouraging. Their degree of analgesia had been much superior to those of the drugs used parenterally.

Pulse and Blood pressure:

There has been no significant effect of the drug on cardiovascular system (Student t test). What ever changes, in respect to pulse and blood-pressure, were there, they were only on account of stress of surgery and anaesthesia.

In the immediate post-operative period there was tachycardia that is most probably on account of pain. Any change in blood pressure is not related with the epidural administration of the drugs. Other workers also did not notice any cardio-vascular variations. Wolfe et al.,(1979) found no significant alterations in heart rate, blood pressure or consciousness level with fentanyl and Kararia et al., (1981) did not notice any fall in blood pressure or change in pulse rate after epidural morphine.

Respiratory rate and Tidal volume:

In our series, no significant change

was observed in the cases of minor lower abdominal, pelvic , perineal and limb surgeries, in respiratory rate and tidal volume with any of the drug used. Similar findings were observed by Kataria et al., 1981 with morphine and by Wolfe et al., 1979 with fentanyl 0.1 mg. for respiratory rate.

Changes were significant particularly with upper abdominal surgeries and lower major abdominal surgeries, where the respiratory rate was increased and tidal volume was reduced at the onset of pain, but 10 and 30 minutes after epidural dose, respiratory rate decreased and tidal volume was found to be raised. With morphine these changes were statistically significant except for the changes in tidal volume after 30 minutes of epidural drug. With pethidine group no change was found to be significant while with fortwin, significant changes were observed in respiratory rate after 30 minutes of injecting drug epidurally. Changes in respiratory rate and tidal volume, 10 and 30 minutes after giving drug were statistically significant (student t test) (Tables 24-29), with fentanyl.

Complications and side effects:

We observed the following complications in our series.

Nausea: It was more with epidural morphine and slightly

less with pethidine 50 mg..Bapat et al.,(1979) in their series found nausea in 17% cases with pethidine, where as we observed in 14.3% cases.

Vomiting: With epidural morphine, vomiting was observed in 12.6% cases. Reiz et al. (1980) reported the incidence of nausea and vomiting in 17% cases in their series.

Retention of urine: Was observed in 25% cases with morphine series and 21.4% cases of pethidine (50 mg.) series. It could not be clearly attributed on account of the drug as post-operative retention of urine is seen following many operations. Other workers - Magora et al., 1980; Reiz et al., 1980 and Andrews and Surendran 1981 also reported the incidence of urinary retention after epidural morphine. They attributed it to the increased tone of detrusor muscle and of the vesical sphincter, thus impending micturition.

Canula discomfort: This had been the most observed distress. It actually did not cause pain but the presence of catheter in the epidural space has always been taken notice of. There had been a feeling of discomfort. The patients reconcilled after its purpose was explained to them.

Moreover this discomfort can be caused by the piercing of ligaments by a thick 16 gauze Tuohy needle, which was used for this purpose.

The incidence of complications has been

much less than when the drugs are used by other routes, as the total dose requirement of the drug is much less. The incidence of side effects is directly proportional to the amount of drug administered.

In none of our cases, itching was observed with epidural morphine as countered by Reiz et al., (1980); Hales (1980) and Andrews and Surendran (1981), in their cases. No case of respiratory depression was encountered, the finding being contrary to those of Glynn et al., (1979); Scott and McClure (1979); Bean, (1980) and Welch, (1981).

None of the case in our series got sensory or motor loss with any drug when given epidurally, coinciding with the findings of Magora et al., 1980, who experimented upon morphine.

Thus in this study we have seen that the epidural administration of analgesic drugs is far too superior in the degree and duration of analgesia in the post-operative phase. There occur no significant cardiovascular alterations. The respiratory rate is not decreased. In case of upper abdominal surgery, there is splintage of the diaphragm on account of pain. The patient is unable to ventilate his lungs effectively. The tidal vulume is affected.

If we keep such cases under conventional

methods of analgesia, significant results are not achieved. With epidural administration of analgesics we have seen that effective analgesia is achieved and better ventilatory conditions are maintained.

Thus the effective achievement of degree and duration of analgesia with much smaller dose in quantity and frequency goes a great way in making this method definitely a superior technique for post-operative analgesia. With the added advantage of having minimum side effects, the procedure becomes still more beneficial.

CONCLUSION

CONCLUSION

On the basis of observations made on 87 cases, studied in the present series, we have drawn the following conclusions :-

(1) The dosage used in this technique is much less than that with other conventional routes.

(2) The degree and duration of analgesia is much more.

(3) The availability of the attending doctors and the nursing staff, is not much needed.

(4) The anxiety of attendants becomes much less as the patient lies comfortably.

(5) Provision of post-operative pain relief, with this method, becomes easier as it has been used for anaesthesia during surgery.

(6) Any significant cardio-vascular alteration does not occur with this technique.

(7) The side-effects are least, as the dose administered is much less.

(8) There is improvement in ventilatory function on account of pain relief in upper-abdominal and thoracic surgeries.

(9) Pethidine, 50 mg. and pentazocine, 15 mg. have been observed to provide best results.

(10) Fentanyl has been foundto be most effective, but the duration of analgesia is too short. It is not suitable for prolonged post-operative pain relief.

(11) The method is simple. It is not habit forming.

(12) The technique needs minimum of armamentarium.

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